THE ASAM

Treatment of Opioid Use Disorder Course

Includes Waiver Qualifying Requirements

Announcements

- You MUST sign in and out on the log of trainees. If you do not sign in AND out, you will not be eligible for the waiver and your name will not be submitted with our attendance report. You must sign in at the beginning of the course and again at the conclusion of the course.
- You can fill out the online waiver form on SAMHSA's website or through their mobile app MATx.
- You have 30 days to complete the online portion of the course if you have not already. Your name will NOT be sent to SAMHSA if you have not completed the online portion. You have until Friday, February 9, 2018, to finish the course.
- To claim your CME, please return to ASAM's e-Learning Center where you took the online portion of the course. You will need to fill out the live portion evaluation before you can claim CME and view your certificate.
- You will need to submit a copy of your certificate to the Center for Substance Abuse Treatment (CSAT) after you submit the online waiver application by emailing it to: infobuprenorphine@samhsa.hhs.gov or by faxing it to: 301-576-5237.

Announcements

- Copies of the slides and other resources are available under "Handouts" where you took the online portion of the course. They are also available on the ASAM website.

- If you have specific questions about the Patient Limit Increase or the recently-passed CARA bill, please email advocacy@asam.org.

- If you are a nurse practitioner or physician assistant, this 8-hour course will count toward the 24-hour education requirement under CARA. ASAM is pleased to offer the additional 16 hours needed free of cost. Please contact education@asam.org to learn how to enroll in the completely online offering. If you are a physician and there are physician assistants and nurse practitioners back in your practice that you would like to get waivered, please contact ASAM for more information on how to get them enrolled.

Faculty Contributors

Daniel P. Alford, MD, MPH, DFASAM *Chair*
Boston University School of Medicine

Sarah Bagley, MD
Boston University School of Medicine

Jeffrey D. Baxter, MD, FASAM
University of Massachusetts Medical School

Colleen LaBelle, BSN, RN-BC, CARN
Boston Medical School

Sharon Levy, MD, MPH
Harvard Medical School
Children's Hospital Boston

Paula J. Lum, MD, MPH, FASAM
University of California – San Francisco

Kelley Saia, MD
Boston University School of Medicine

Edwin A. Salsitz, MD, DFASAM
Mount Sinai Beth Israel Medical Center

Andrew J. Saxon, MD, FASAM
University of Washington, VA Puget Sound

Alexander Y. Walley, MD, MSc
Boston University School of Medicine

The ASAM Treatment of Opioid Use Disorder Course

Disclosure Information

Edwin Salsitz, MD, DFASAM

No Disclosures

Doug Burgess, MD

No Disclosures

Claiming CME & Obtaining a Waiver

To claim CME for The ASAM Buprenorphine Course, please return to the e-Learning Center.

To qualify for authority to prescribe buprenorphine for the treatment of opioid dependence, the Drug Addiction Treatment Act of 2000 requires physicians to complete **not less than 8 hours of training**. The American Society of Addiction Medicine cannot confirm training for those who arrive late or depart before the completion of the course.

The combined online enduring material and live activity will provide the required 8 hours needed to obtain the waiver to prescribe buprenorphine in office-based treatment of opioid use disorders.

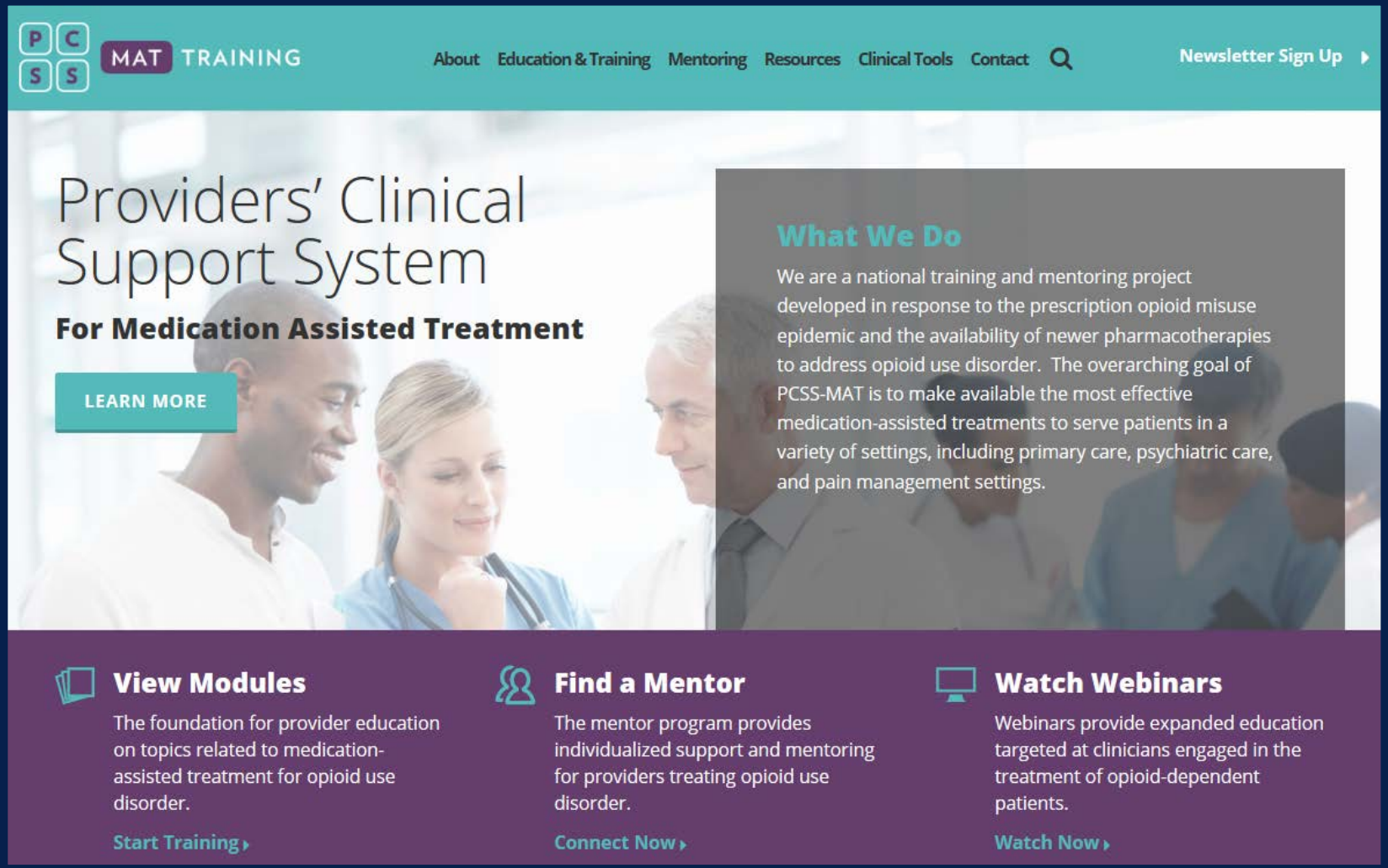
****IF YOU HAVE NOT COMPLETED THE ONLINE PORTION OF THE COURSE, YOU HAVE 30 DAYS TO DO SO AFTER COMPLETION OF THE LIVE COURSE/WEBINAR****

Course Materials and Resources

Find a list of these resources and more on the e-Learning Center and on **www.asam.org**

- The ASAM National Practice Guidelines for the Use of Medications in the Treatment of Addiction Involving Opioid Use
- Prescribers Clinical Support System for Medication Assisted Treatment
- SAMHSA
- DATA Physician Locator
- Waiver Notification Form
- Agency for Healthcare Research and Quality
- NIDA
- DEA
  A Guide for Law Enforcement on Buprenorphine
- Handbook of Office-Based Buprenorphine Treatment of Opioid Dependence

pcssmat.org

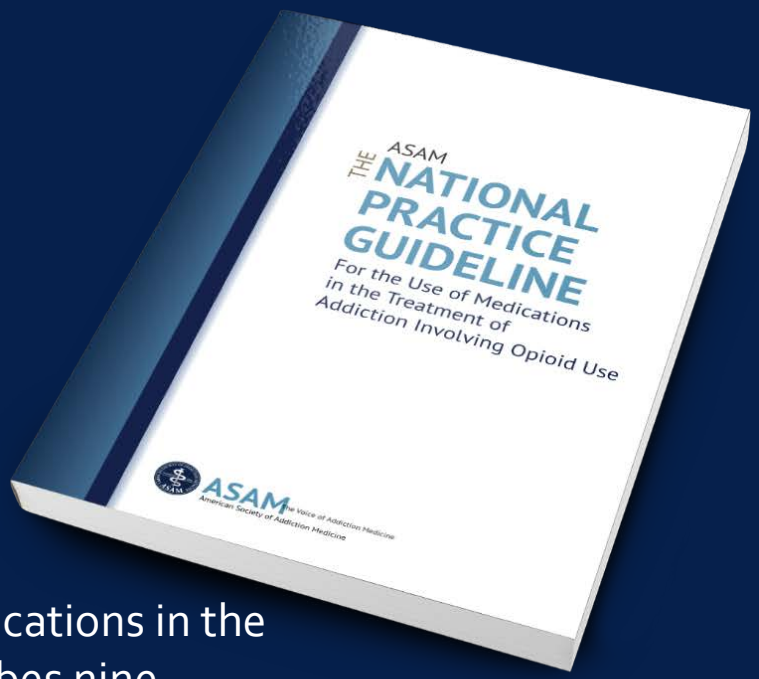


ASAM American Society of Addiction Medicine

THE ASAM Treatment of Opioid Use Disorder Course
Includes waiver qualifying requirements

ASAM National Practice Guideline

NOW AVAILABLE – **National Practice Guideline** – for the Use of Medications in the Treatment of Addiction Involving Opioid Use



The National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use describes nine measures that address key areas of concern in health care delivery which, when implemented, will have the potential to improve patient and health care outcomes.

National Practice Guideline: http://bit.ly/1CrCPFv

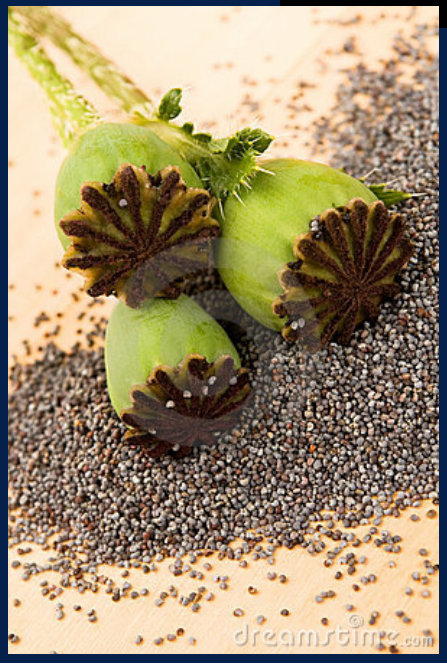
Agenda

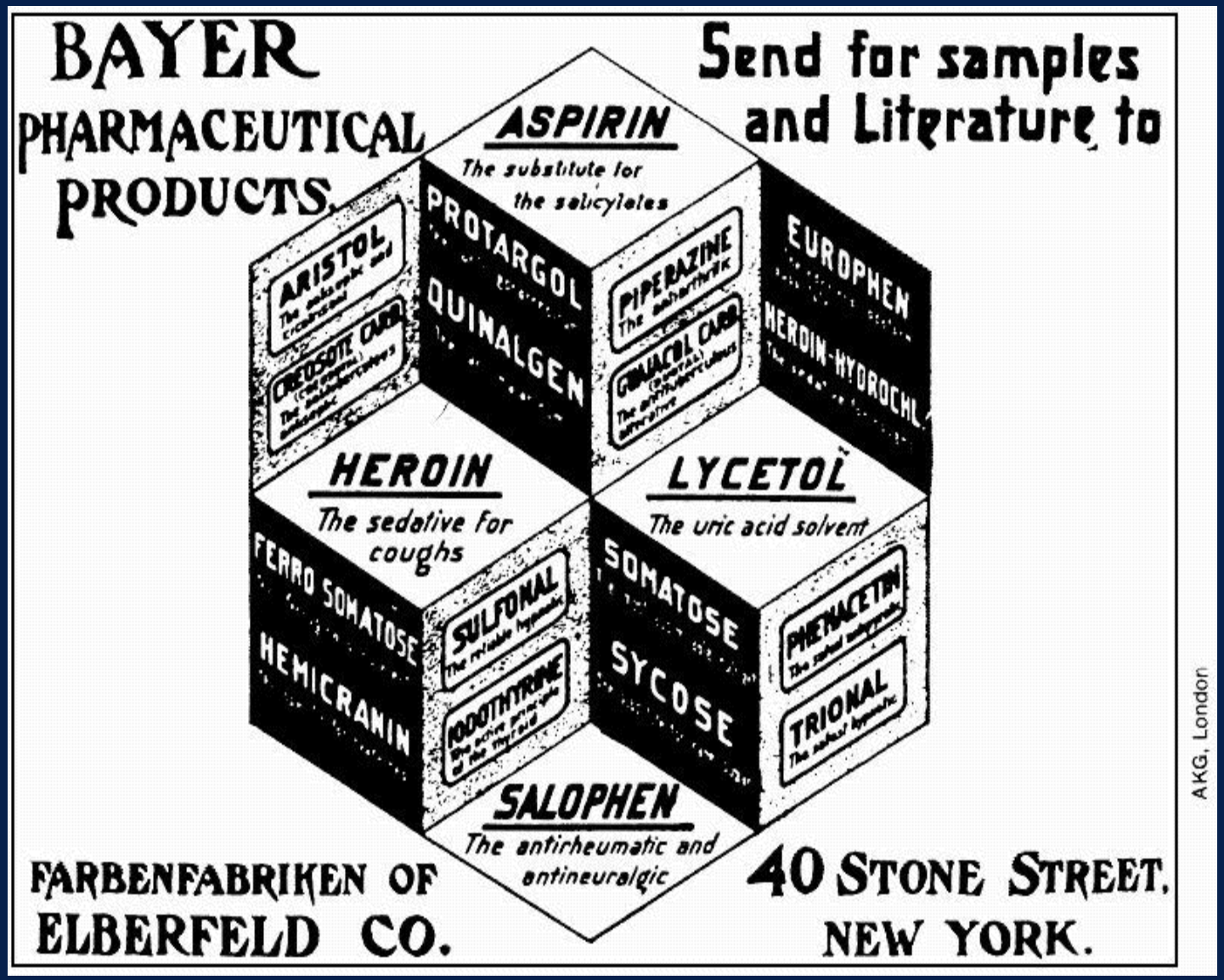
- 8:00 am -8:05 am **Welcome and Introductions**
- 8:05 am -8:30 am **The Science and The Law**
- 8:30 am - 10:00 am **Implementing Office-Based Opioid Treatment**
- 10:00 am - 10:15 am Refreshment Break
- 10:15 am -10:50 am **Special Populations**
- 10:50 am – 12:00 pm **Case Studies with Q&A**
- 12:00 pm - 12:30 pm Completing the Online Waiver Form & Final Q&A

Introduction

The **Opioid Epidemic** in the USA

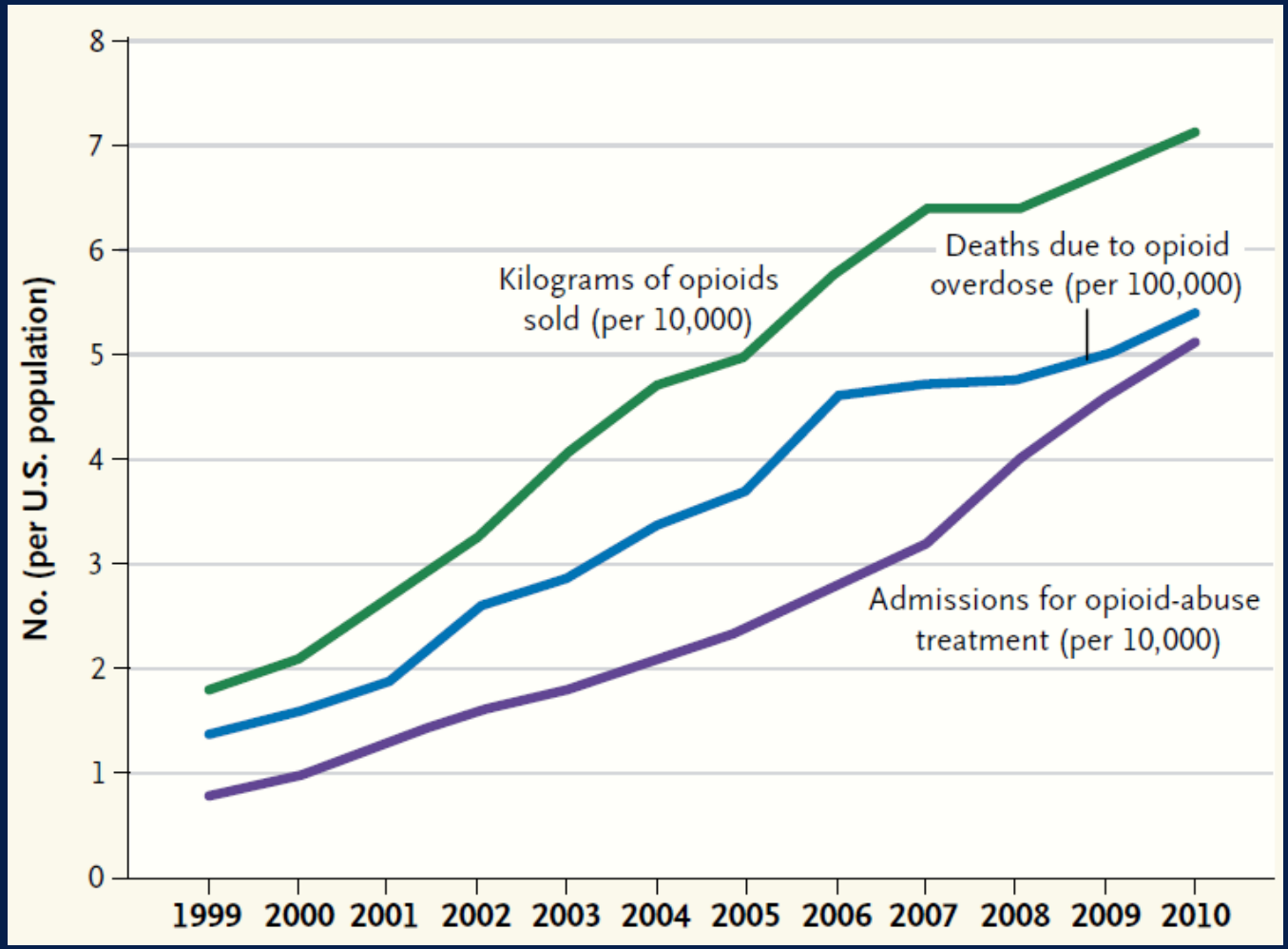
Papaver somniferum
Photo by Eric Clausen, © 2000 Erowid.org




BAYER
PHARMACEUTICAL PRODUCTS.
Send for samples and Literature to
ASPIRIN
The substitute for the salicylates
ARISTOL
CREOSOTE CARB.
PROTARGOL
QUINALGEN
PIPERAZINE
GUAIACOL CARB.
EUROPHEN
HEROIN-HYDROCHL.
HEROIN
The sedative for coughs
LYCETOL
The uric acid solvent
FERRO SOMATOSE
HEMICRANIN
SULFONAL
IODOTHYRINE
SOMATOSE
SYCOSE
PHENACETIN
TRIONAL
SALOPHEN
The antirheumatic and antineuralgic
FARBENFABRIKEN OF ELBERFELD CO.
40 STONE STREET, NEW YORK.

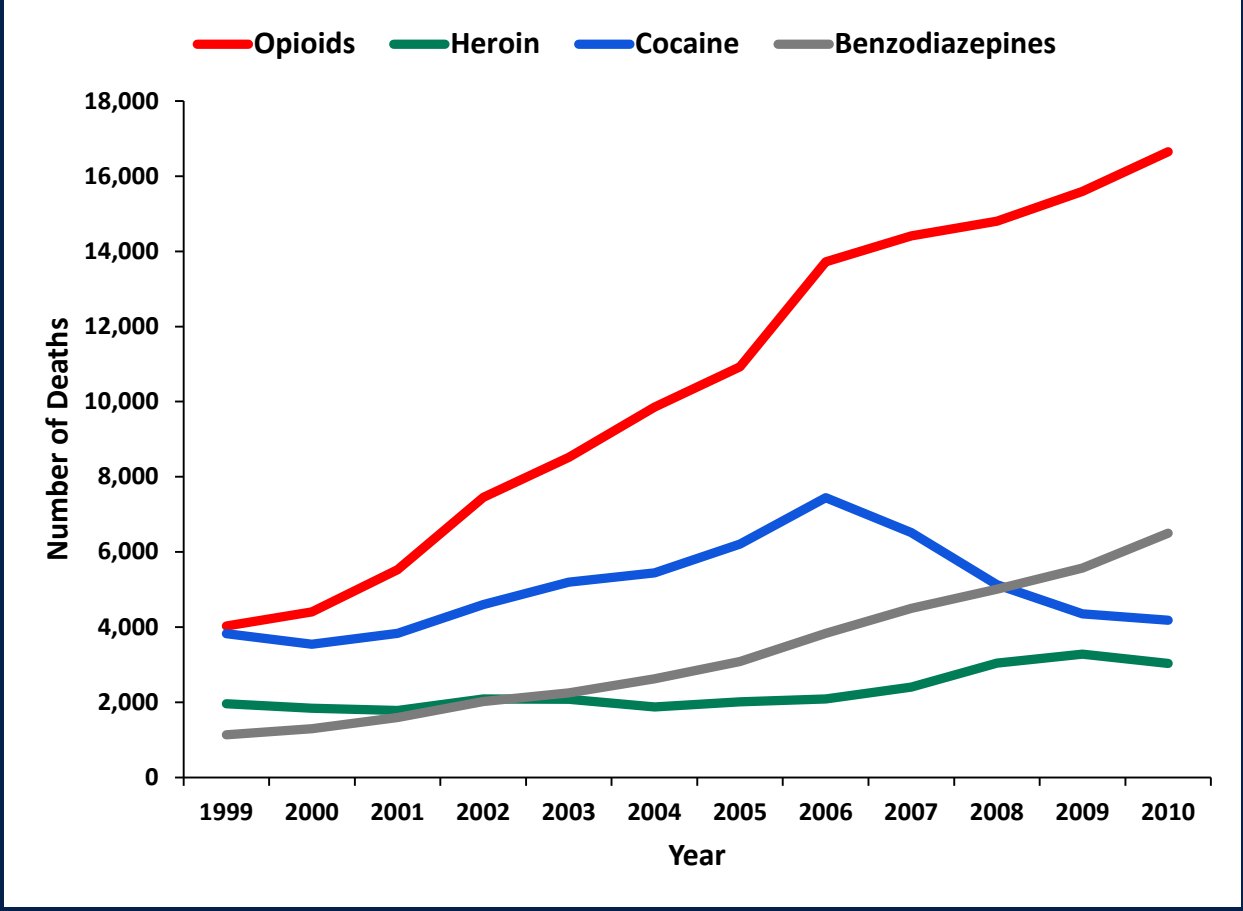
AKG, London

Prescription Opioid Trends: 1999-2010

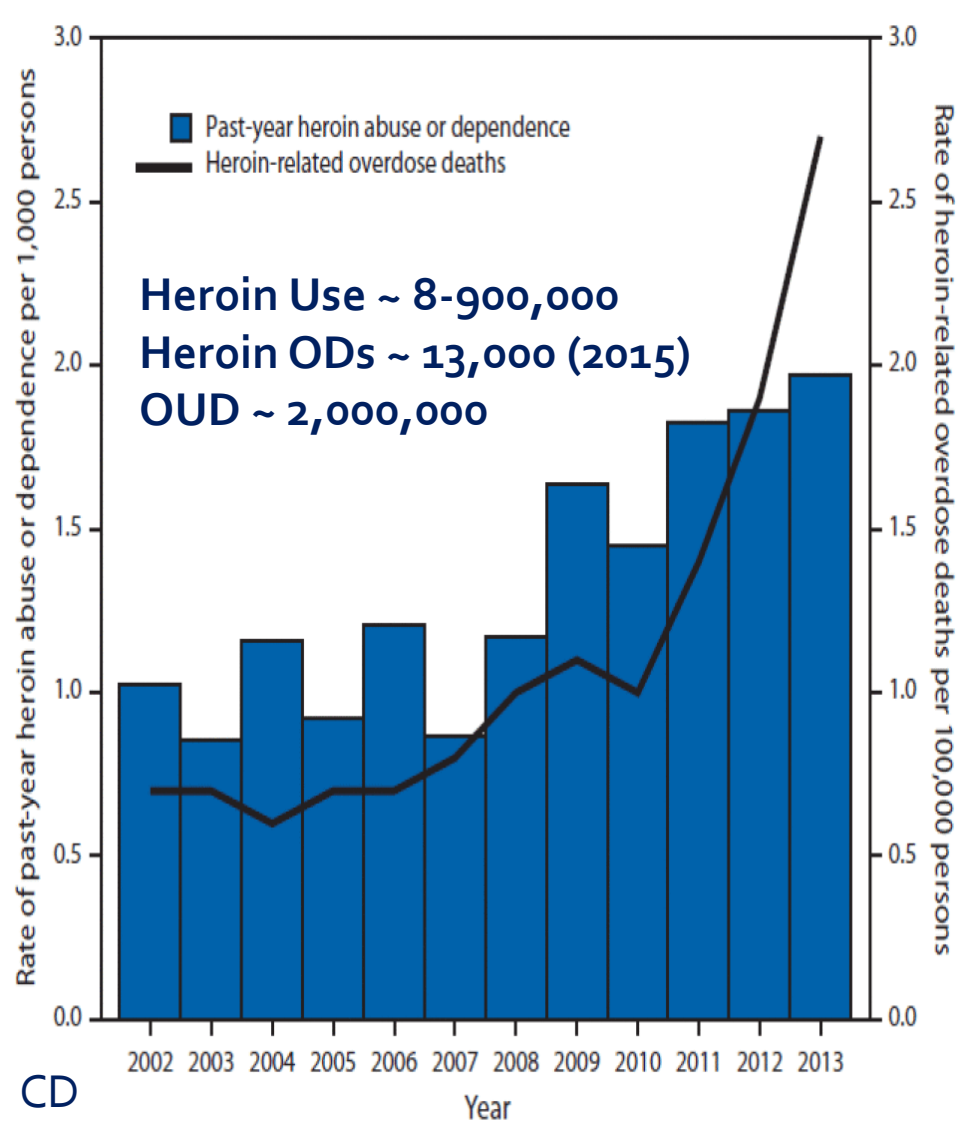


National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders System of the DEA; Treatment Episode Data Set

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

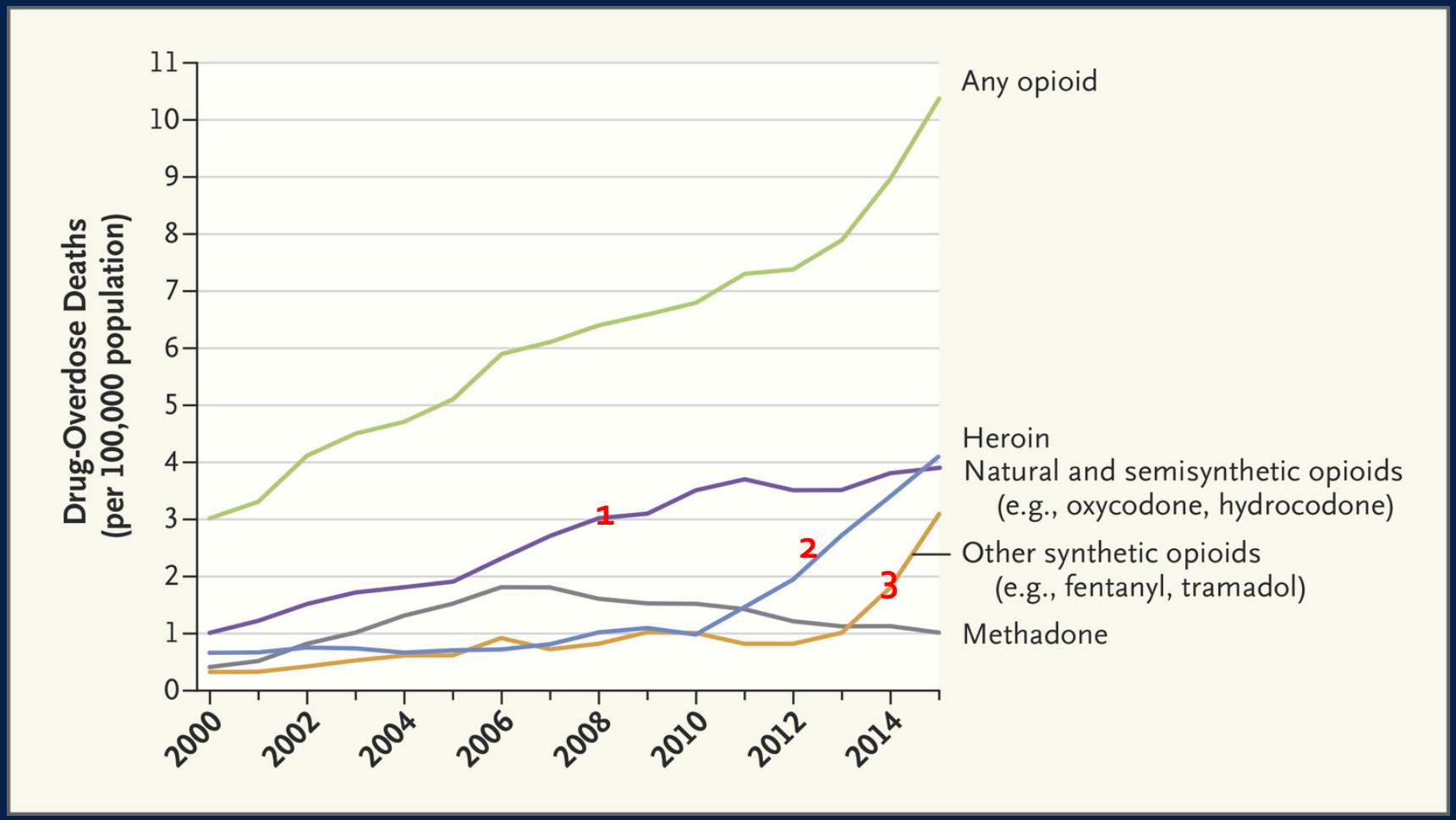


CDC, National Center for Health Statistics, National Vital Statistics System, CDC Wonder. Updated with 2010 mortality data.


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

ASAM American Society of Addiction Medicine

Treatment of Opioid Use Disorder Course
Includes waiver qualifying requirements

Boonshoft School of Medicine
WRIGHT STATE UNIVERSITY

RESEARCH UPDATE ON FENTANYL OUTBREAKS IN THE DAYTON, OH AREA:

Acryl Fentanyl and Furanyl Fentanyl Commonly Found In Overdose Death Cases

UPDATE 04/28/2017

DAYTON, OHIO. The Dayton area (Montgomery County, Ohio) has recently experienced dramatic increases in heroin and other opioid-related problems. Unintentional drug overdose deaths increased significantly from 127 in 2010 to 264 in 2014. In 2016, there were 349 overdose deaths in Montgomery County, and 251 of them screened positive for fentanyl. Preliminary data from 2017 indicate continuing increases in overdose deaths.

THE STUDY. The research project (R21DA042757) to characterize fentanyl outbreaks in the Dayton, Ohio, area builds on interdisciplinary collaboration between the researchers at the Center for Interventions, Treatment and Additions Research and the Department of Chemistry at Wright State University, and longstanding partnership with the Montgomery County Coroner's Office/Miami Valley Regional Crime Lab (MCCO/MVRC) and Public Health-Dayton & Montgomery County.

TESTING. The research project developed and validated a qualitative and quantitative liquid-chromatography mass spectrometry (LC-MS/MS) assay for 24 fentanyl analogs/metabolites in biological matrixes (human blood and urine samples):

1-3-Methylfentanyl; 4ANPP; Acetyl Fentanyl; Acetyl Fentanyl 4-Methylphenethyl; Acryl fentanyl; AH7921; Alfentanil; Beta-Hydroxythiofentanyl; Butyryl Fentanyl/Isobutyryl Fentanyl; Butyryl Norfentanyl; Carfentanil; Despropionyl Para-Fluorofentanyl; Fentanyl; Furanyl Fentanyl; Furanyl Norfentanyl; Norfentanyl; Para-Fluorobutyryl/4-Fluoroisobutyrylfentanyl; Para-Methoxyfentanyl; Remifentanil; Remifentanil Metabolite; Sufentanil; U-47700; Valeryl Fentanyl

2 Minutes: 3A4

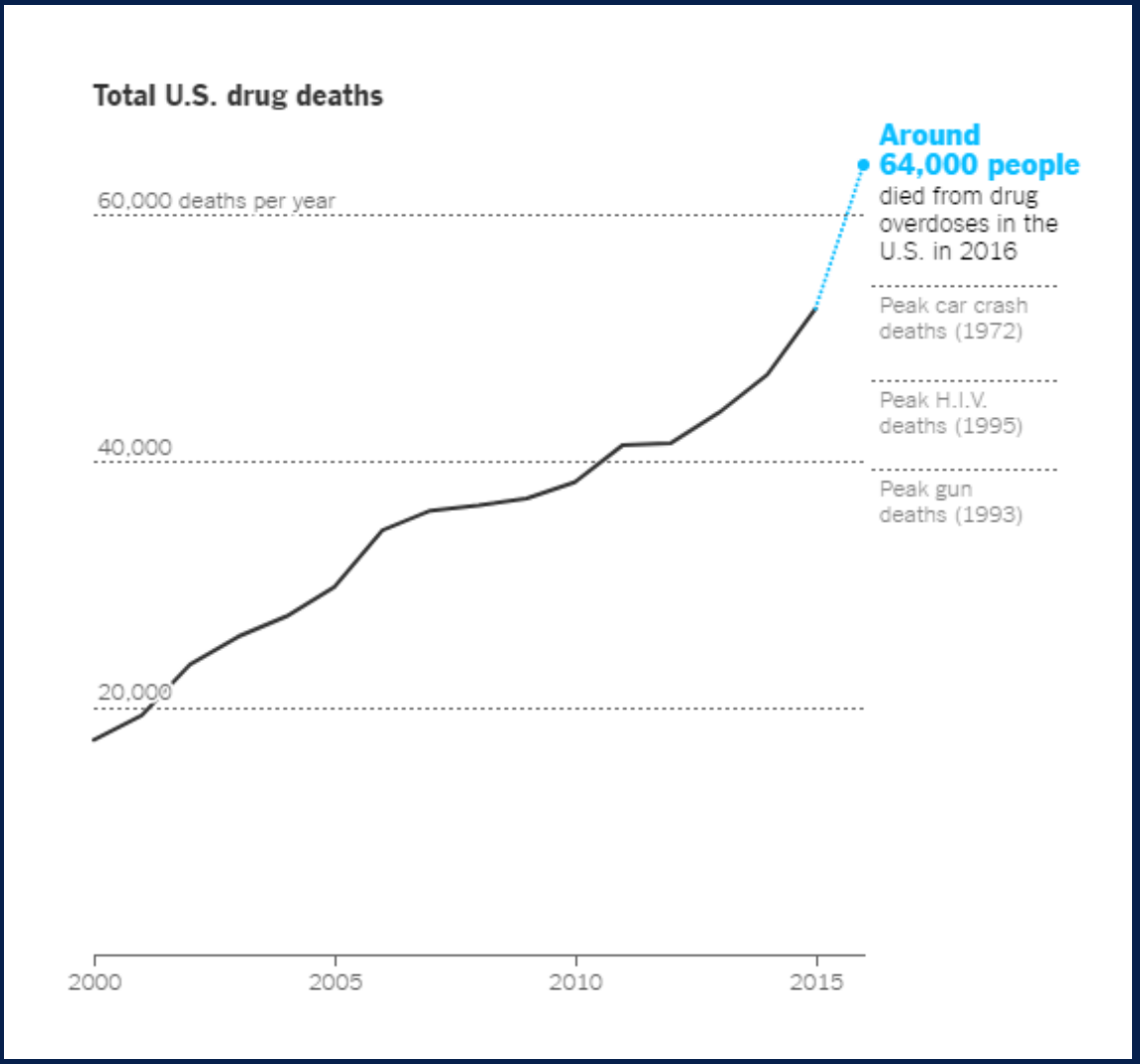
Synthetic opioids/fentanyl analogues/metabolites	A. All cases (N=100)	B. Acryl Fentanyl Positives (N=56)	C. Furanyl Fentanyl Positives (N=39)
Fentanyl	99 (99%)	56 (100%)	39 (100%)
Norfentanyl	64 (64%)	39 (70%)	26 (67%)
Acryl fentanyl	56 (56%)		25 (64%)
Despropionylfentanyl	46 (46%)	26 (46%)	32 (82%)
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

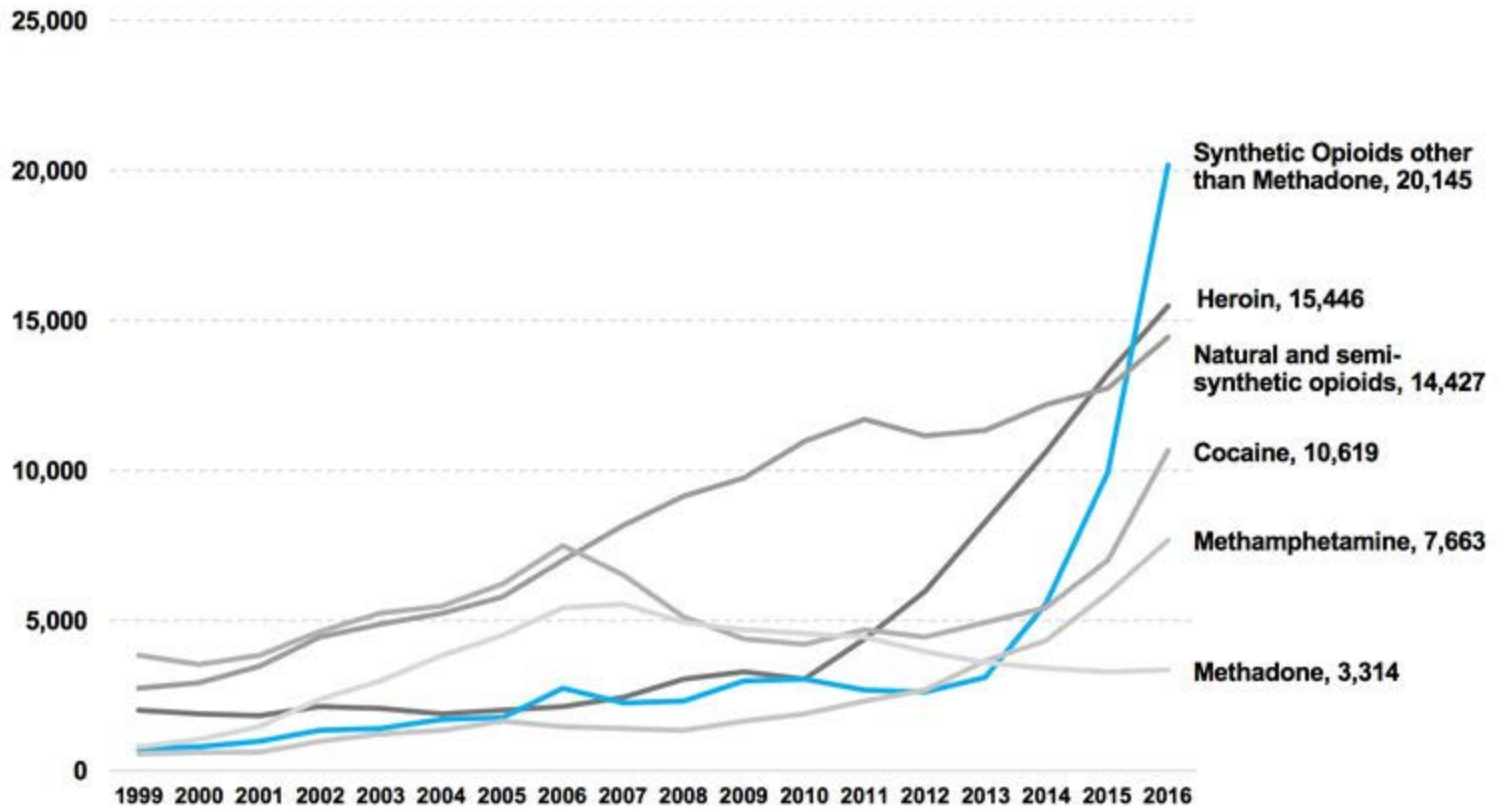
Fentanyl Chest Wall Rigidity

- First Reported in 1953 in anesthesia literature
- Skeletal Muscle Rigidity: Chest Wall Most Common
- Most common with fentanyl and its congeners (lipid solubility)
- Most common with rapid IV administration
- Activation of the coerulospinal noradrenergic pathway, following mu receptor activation in LC
- Not dose related
- Reversed with naloxone (IV route in literature)
- Ventilatory Support
- Low or Absent Norfentanyl (appears in 2 minutes: CYP3A4(Inhb)

Burns, G et al Clinical Toxicology, Vol 54, No 5, 420-23, 2016


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

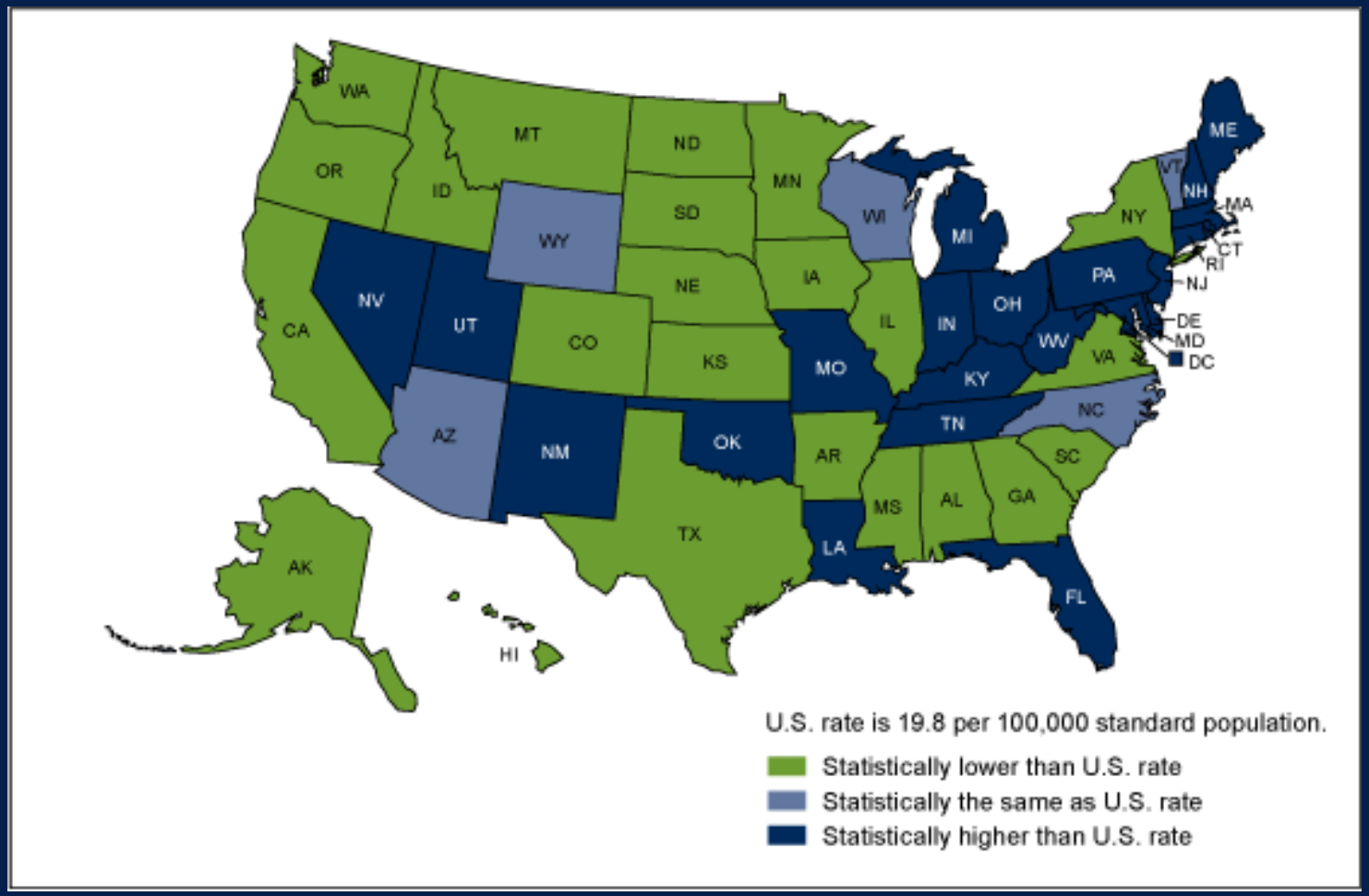


Lethal Dose

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

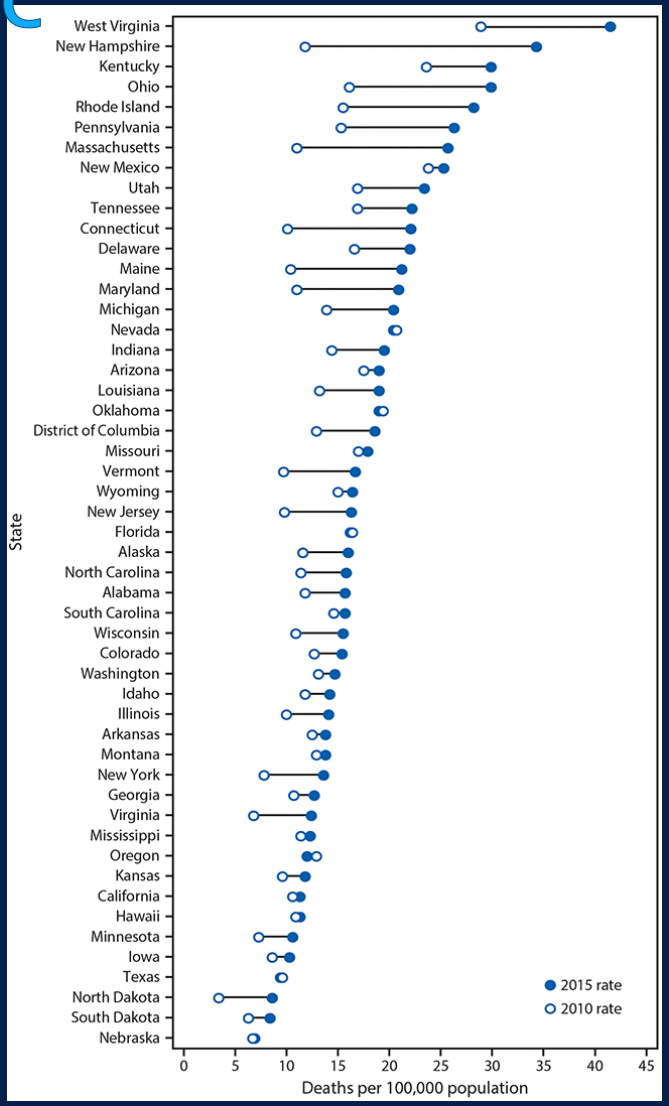
Lethal doses of heroin compared to "synthetic" opioids.
New Hampshire State Police Forensic Lab

Drug Overdose Deaths—2016



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

Age-adjusted rate* of drug overdose deaths, by state — 2010 and 2015 CDC



NEW YORK CITY DEPARTMENT OF HEALTH
AND MENTAL HYGIENE
Mary T. Bassett, MD, MPH
Commissioner

FOR IMMEDIATE RELEASE
Thursday, June 1, 2017
(347) 396-4177

HEALTH DEPARTMENT WARNS NEW YORKERS ABOUT COCAINE LACED WITH FENTANYL; OCCASIONAL USERS AT HIGH RISK OF OVERDOSE

In 2016, 37 percent of overdose deaths involved cocaine and fentanyl without heroin, up from 11 percent in 2015

Last year more than 1,300 New Yorkers died of a drug overdose, and nearly half (44 percent) of those deaths involved fentanyl

June 1, 2017 – The Health Department today announced that fentanyl is being increasingly found in cocaine-involved overdose deaths. Fentanyl, an opioid 50 to 100 times more powerful than morphine, is being mixed in illicit drugs – often without the buyer's knowledge. The presence of fentanyl in any illicit drug, including cocaine, increases the risk of overdose. In 2016, 37 percent of overdose deaths involved cocaine and fentanyl without heroin, up from 11 percent in 2015. In 2016, nearly half (44 percent) of all overdose deaths involved fentanyl, up from 16 percent in 2015. The Health Department also issued a Health Advisory to 40,000 medical professionals with information on how to educate patients, particularly those who may use cocaine occasionally, about the increased overdose risk posed by fentanyl. In April, Mayor

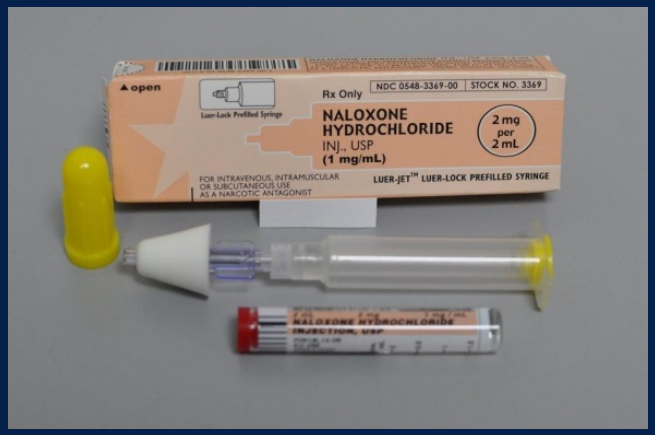
Substance Use Disorders in Perspective

- Alcohol Use Disorder: ~ 20 million affected
- Alcohol Related Deaths: ~100,000 per year

- Tobacco Use Disorder: ~20% population > 18yo
- Tobacco Related Deaths: ~450,000 per year

- Opioid Use Disorder: ~ 2.1 million

Naloxone Formulations



Module I

The Science and The Law
The Essentials

This module will review…

- Drug Addiction Treatment Act of 2000 (DATA 2000)
- Opioid neurobiology and pharmacology
- Treatment with medications

Drug Addiction Treatment Act of 2000 (DATA 2000)

- Allows a **waivered physician** (DEA "X" number) to **prescribe** an opioid to a patient with an opioid use disorder for the treatment of the opioid use disorder, with certain restrictions…
- OBOT: Office-Based Opioid Therapy

Practitioner Requirements

- "Qualifying physician"
  - Board certified in addiction psychiatry
  - ASAM certified (ABAM)
  - AOA certified
  - Investigator in buprenorphine clinical trials
  - Completed 8 hours of training in approved course
- NP or PA (Comprehensive Addiction and Recovery Act of 2016)
- Can certify linkages to ancillary and counseling services
- Patient limit for physicians
  - 30 patients
  - 100 patients
  - 275 patients

DATA 2000, restrictions:

- Physician qualifications
  - Certified in addiction medicine/psychiatry, or
  - Have 8 hours of training by AMA, AAAP, ASAM, AOA, APA
- Certify capacity to refer the patients for appropriate counseling and other appropriate ancillary services
- Medication qualifications
  - Approved by FDA for use in treating addiction (opioid use disorder)
  - DEA schedule III, IV, or V (methadone is schedule II)
  - Buprenorphine and Buprenorphine/naloxone SL tablets, film and depot rods FDA approved and DEA schedule III, and are the only medications fitting these restrictions

Patient Limits

- **Number of patients**
  - 30 patients per physician during the 1st year of the waiver
    - After the 1st year, 100 patients per physician – a new waiver must be obtained
    - After 1 year at 100 patients, the physician can go up to 275 if they/treatment center meet certain criteria
  - Waivered PAs and NPs are able to prescribe up to 30 patients
  - Patient remains on your census until the last prescription has run out
  - Hospitalized patients can be administered buprenorphine by a non-waivered physician

https://www.samhsa.gov/sites/default/files/programs_campaigns/medication_assisted/understanding-patient-limit275.pdf

Opioid Pharmacology and Neurobiology

Opiates and Opioids

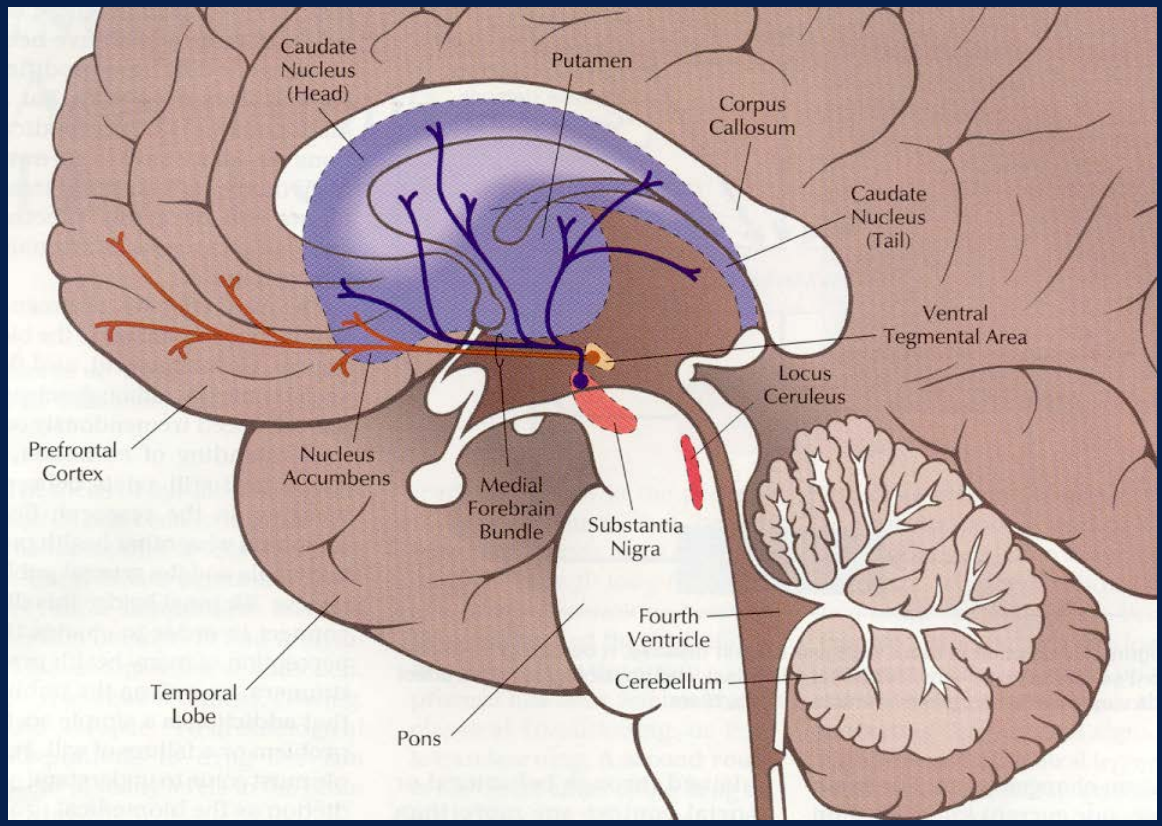
- **Opiates** are present in opium e.g. morphine, codeine, thebaine
- **Opioids** are manufactured as

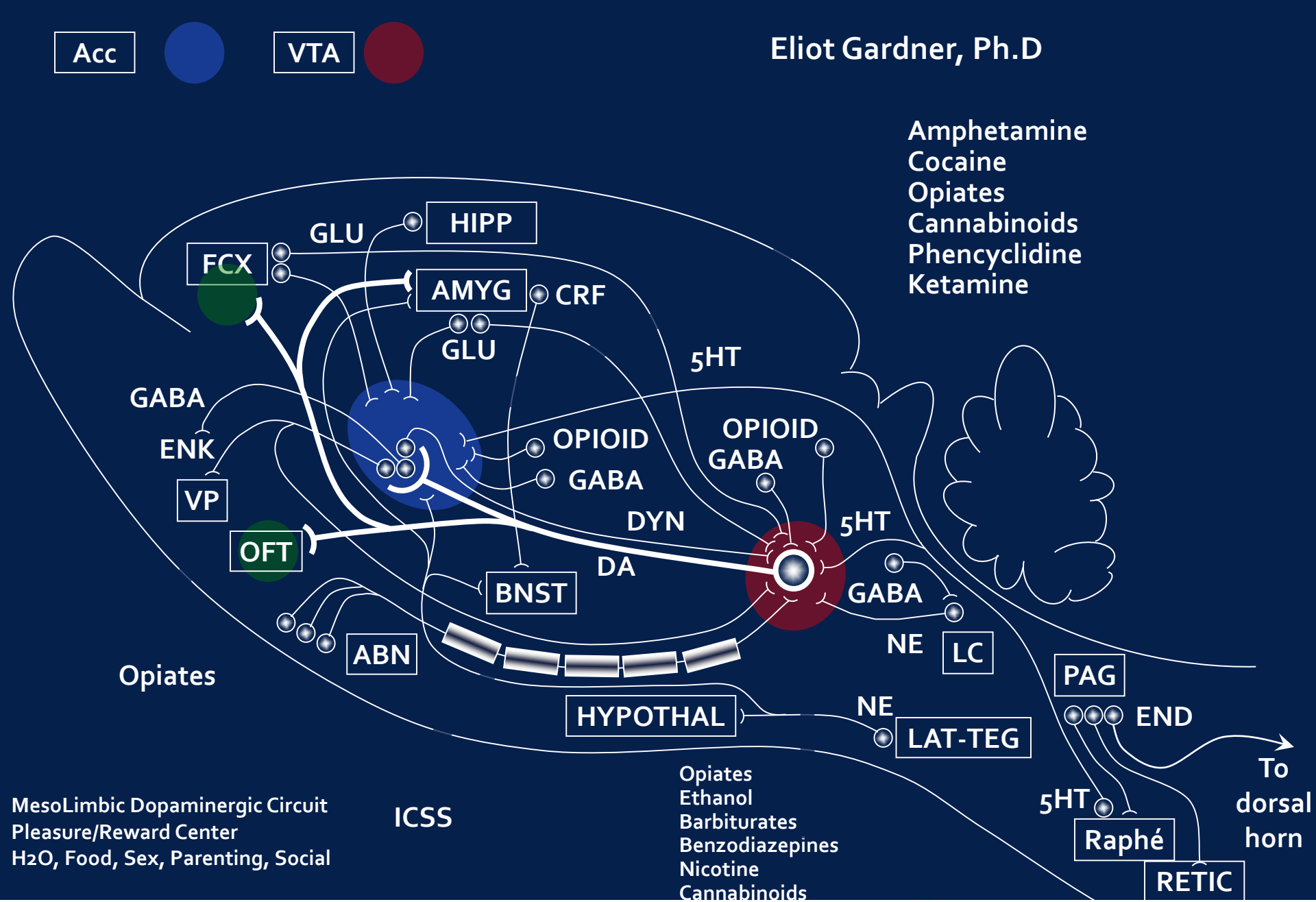
  - **Semi-synthetic opioids:** derived from an opiate e.g. heroin from morphine, oxycodone, hydrocodone
  - **Synthetic opioids:** completely synthesized to have function similar to natural opiates e.g. methadone, fentanyl, buprenorphine

Reward/Reinforcement

Reward/Reinforcement is in part controlled by mu receptors in the Reward Pathway:

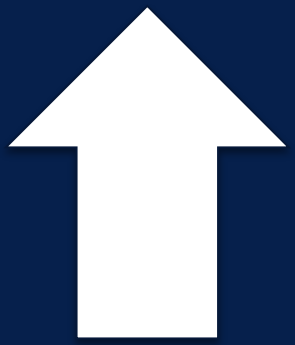
- Ventral Tegmental Area (VTA)
- Nucleus Accumbens with projections to Prefrontal Cortex
- Dopaminergic system





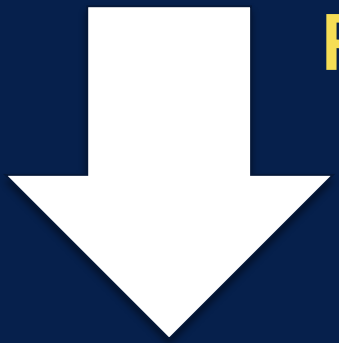
Opioid Tolerance & Physical Dependence

Both tolerance and physical dependence are physiological adaptations to chronic opioid exposure



Tolerance:

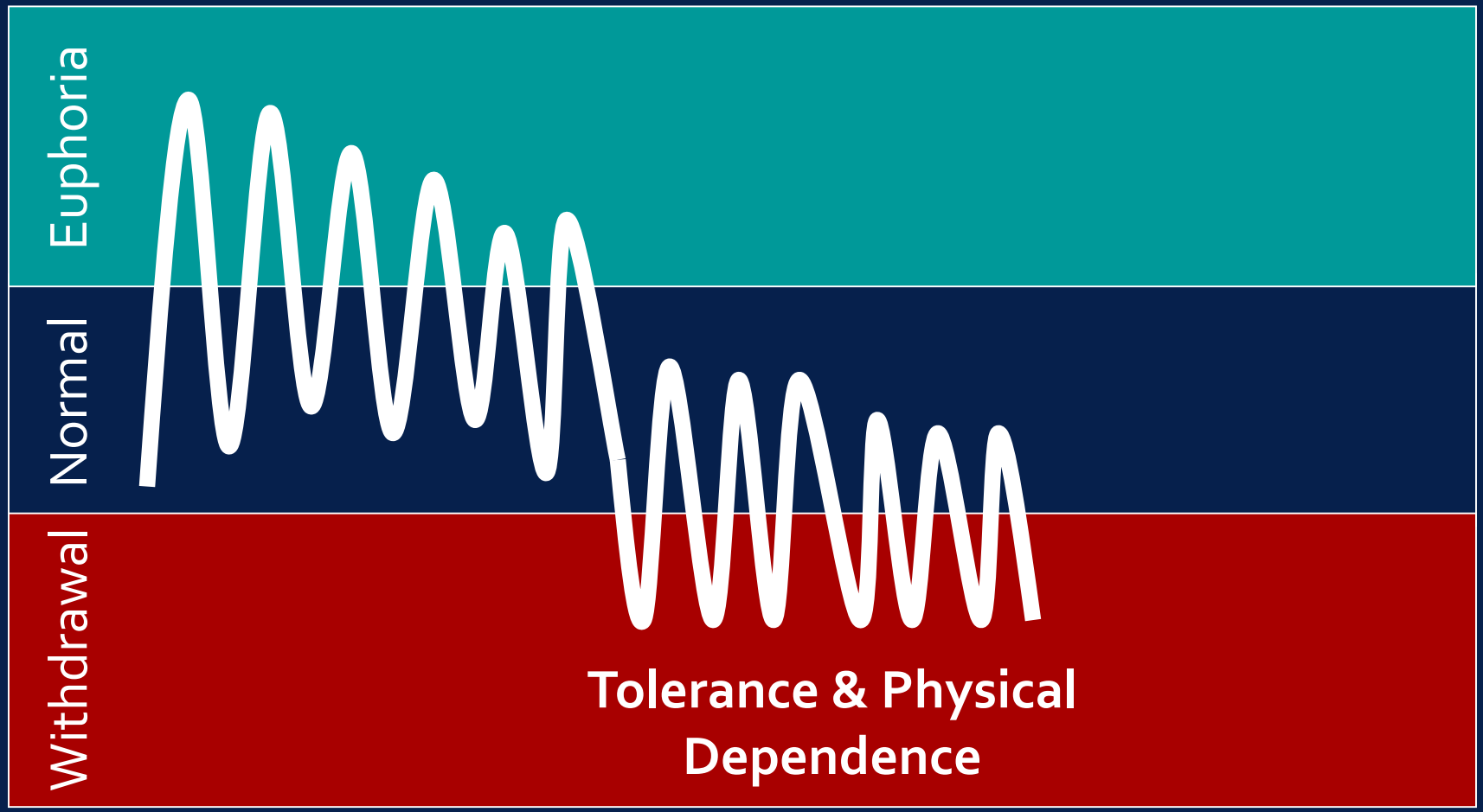
- Increased dosage needed to produce specific effect
- Develops readily for CNS and respiratory depression



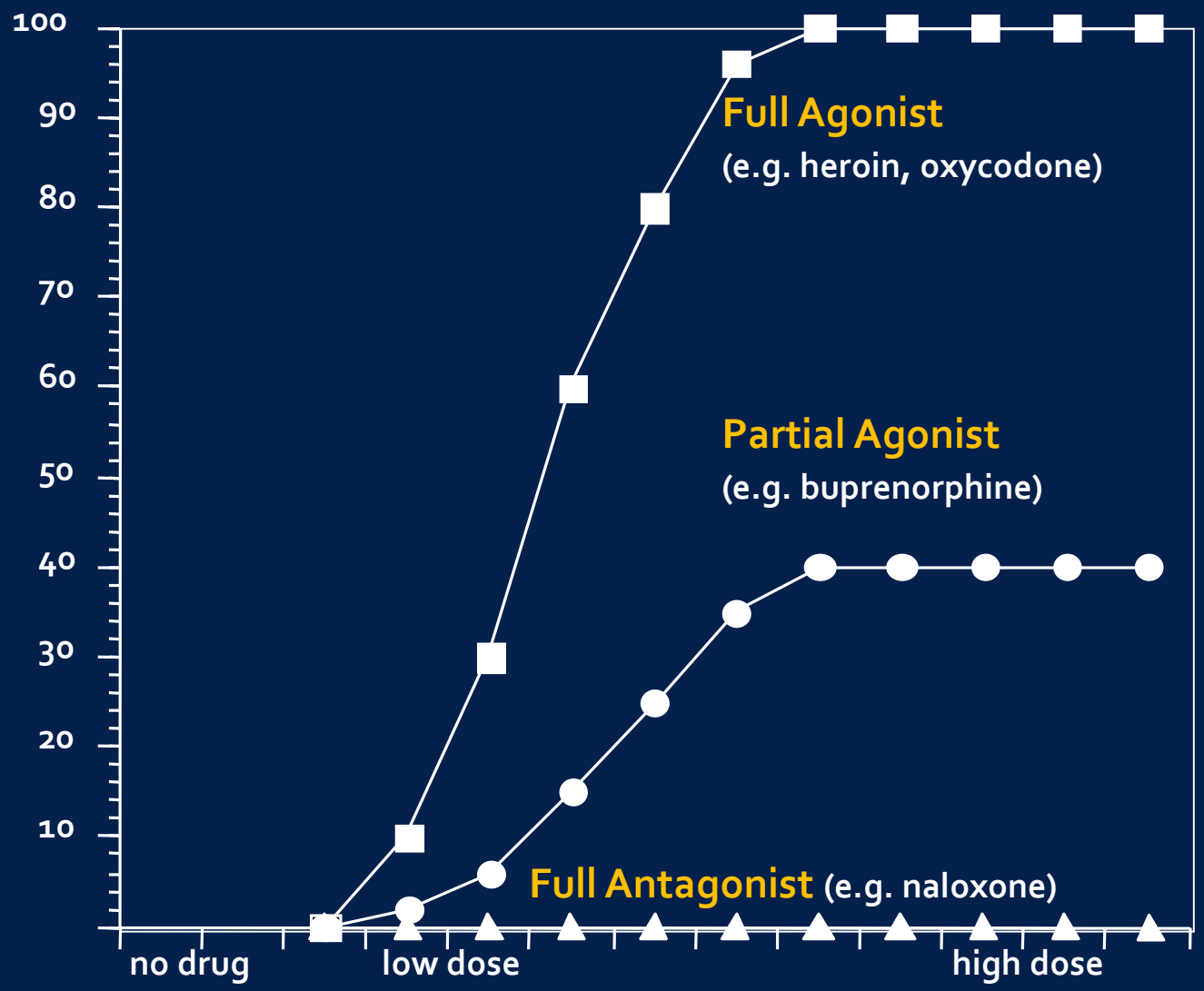
Physical Dependence:

- Signs and symptoms of withdrawal by abrupt opioid cessation, rapid dose

Natural History of Opioid Use Disorder



Opioid Agonists and Antagonists



Acute Opioid Withdrawal

Grade	Symptoms / Signs
0	Anxiety, Drug Craving
1	Yawning, Sweating, Runny nose, Tearing eyes, Restlessness Insomnia
2	Dilated pupils, Gooseflesh, Muscle twitching & shaking, Muscle & Joint aches, Loss of appetite
3	Nausea, extreme restlessness, elevated blood pressure, Heart rate > 100, Fever
4	Vomiting / dehydration, Diarrhea, Abdominal cramps, Curled-up body position

Clinical Opiate Withdrawal Scale (COWS):

pulse, sweating, restlessness & anxiety, pupil size, aches, runny nose & tearing, GI sx, tremor, yawning, gooseflesh

5-12 mild,
13-24 moderate
25-36 moderately severe
>36 severe

Spontaneous Acute Opioid Withdrawal

- Develops spontaneously in a physically dependent person suddenly stops, or markedly decreases, the opioid
- Severity is usually less with longer half-life drugs
- Duration depends on half-life of opioids person is physically dependent on

	Onset	Peak	Duration
Heroin	4 - 6 hours	~3 days	4 - 7 days
Methadone	1 - 2 days	~7 days	12 - 14 days

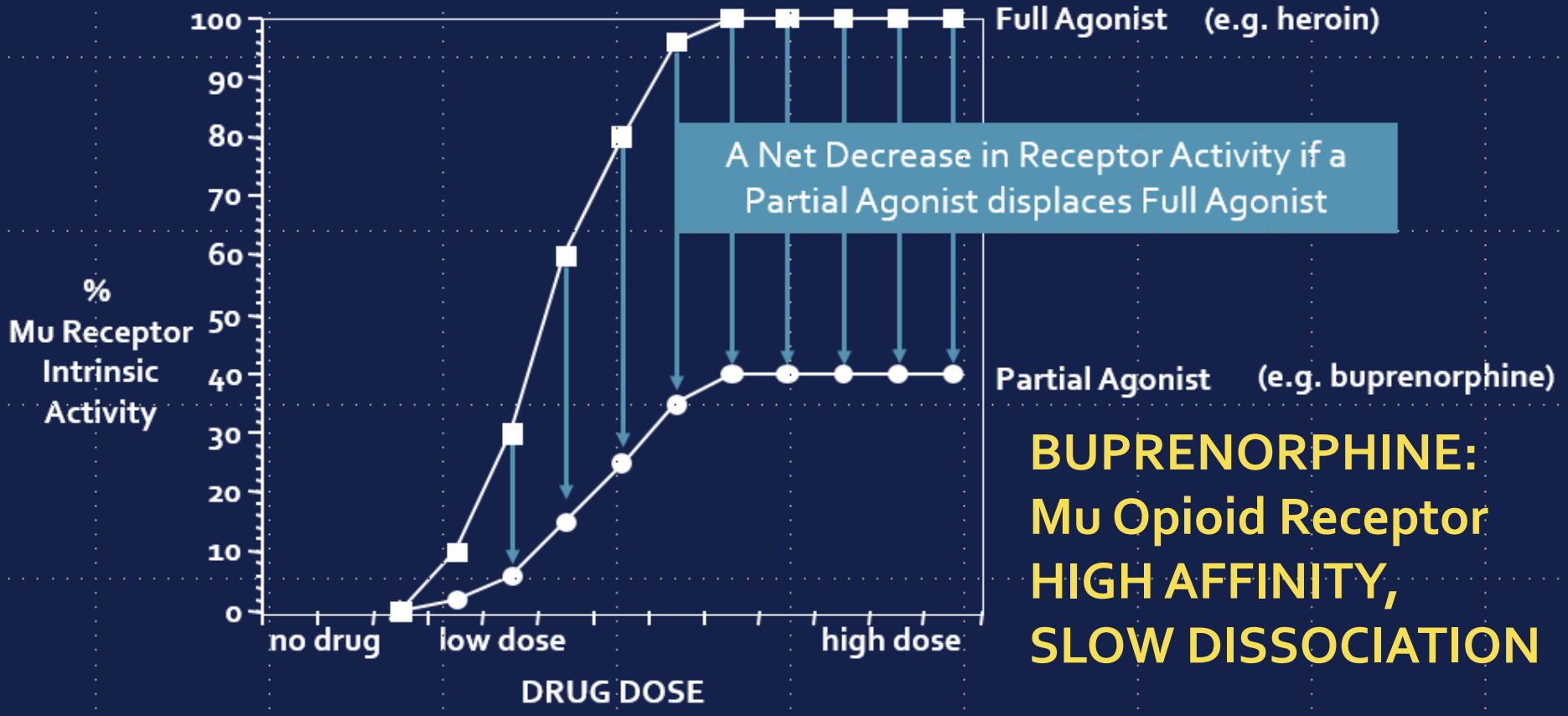
Precipitated Acute Opioid Withdrawal

- Precipitated in a physically dependent person, by administration of either:
  - an opioid antagonist (e.g. naloxone, naltrexone) or
  - an opioid partial agonist (e.g. buprenorphine)
- Qualitatively similar to spontaneous withdrawal but faster onset
- Duration depends upon half-life of medication causing the withdrawal

	Onset	Peak	Duration
Naloxone	minutes	minutes	~20 minutes
Naltrexone	minutes	minutes	1 – 2 days
Buprenorphine	minutes	minutes	1 – 2 days

Buprenorphine is a Partial Agonist

- Buprenorphine will precipitate withdrawal when it displaces full agonist off the receptors



BUPRENORPHINE: Mu Opioid Receptor HIGH AFFINITY, SLOW DISSOCIATION

Treatment Medications Efficacy and Safety

Medically Supervised Withdrawal Management

- Low rates of retention in treatment
- High rates of relapse post-treatment
  - < 50% abstinent at 6 months
  - < 15% abstinent at 12 months
- Withdrawal management is not treatment, it is just the start of treatment
- Increased rates of overdose due to decreased tolerance

O'Connor PG. *JAMA.* 2005.
Mattick RP, Hall WD. *Lancet.* 1996.
Stimmel B et al. *JAMA.* 1977.

Reasons for Relapse

- Protracted abstinence syndrome (chronic withdrawal)
  - Generalized malaise, fatigue, insomnia
  - Poor tolerance to stress and pain
  - Opioid craving
- Conditioned cues (triggers)
- Priming with small dose of drug

Kleber H et al. *Dialogues Clin Neurosci*. 2007.

Medications to Treat Opioid Use Disorder

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)

Medication Comparison

	Methadone	Buprenorphine	ER Naltrexone
Pharmacology	Full agonist	Partial agonist	Full agonist
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

Kampman, K. et al. (2015). *The ASAM National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opiod Use*. Retrieved from http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24

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	+++	++	+

Kampman, K. et al. (2015). *The ASAM National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opiod Use*. Retrieved from http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24

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

Kampman, K. et al. (2015). *The ASAM National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opiod Use*. Retrieved from http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24

Oral Naltrexone Efficacy

- Oral naltrexone
  - Duration of action 24-48 hours
  - FDA approved 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

Injectable Naltrexone (XR-NTX)*

- Multicenter (13 sites in Russia)
  - DB RPCT, 24 wks, n=250 w/ opioid dependence
  - XR-NTX vs placebo, all offered biweekly individual drug counseling
  - Increased weeks of confirmed abstinence (90% vs 35%)
  - Increased patients with confirmed abstinence (36% vs 23%)
  - Decreased craving (-10 vs +0.7)
- Two recent studies showed similar effectiveness for XR-NTX and daily buprenorphine-naloxone (BUP-NX)
  - More difficult to start patients on XR-NTX than BUP-NX

*No Black Box LFTs Warning Label for IM formulation

Krupitsky E et al. *Lancet.* 2011.

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): A multicentre, open-label, randomised controlled trial. Lee J.D. et. Al. (2017) *The Lancet.*

Naltrexone: Benefits

Benefits

- Good for patients who do no want agonist or partial agonist therapy
- No risk of diversion (not a controlled substance)
- No risk of overdose by drug itself
- Can be administered in any setting (OBOT or OTP)
- Long-acting formulation
- Treats both opioid use disorder and alcohol use disorder

Kampman, K. et al. (2015). *The ASAM National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use*. Retrieved from http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24

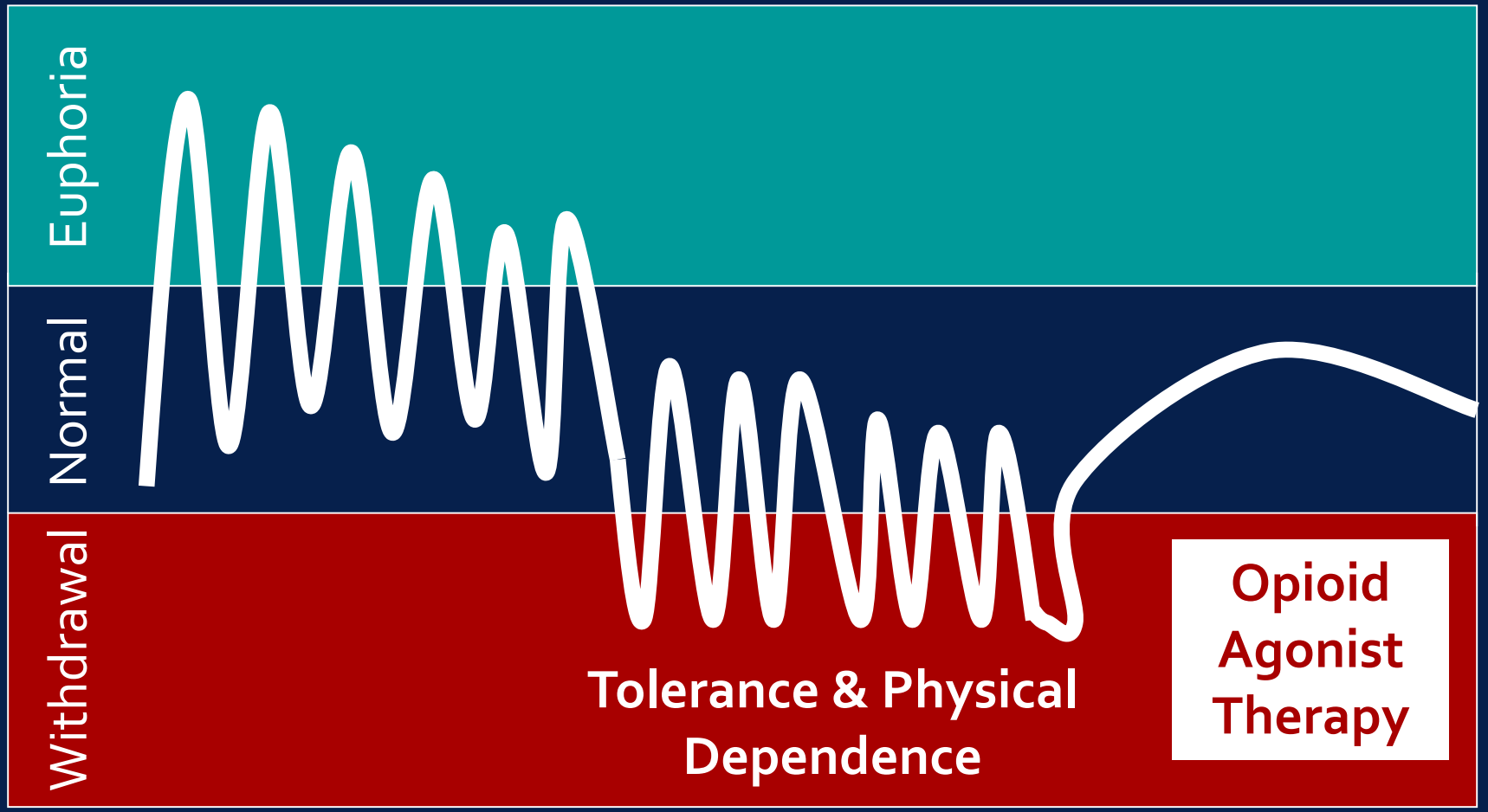
Naltrexone: Limitations

Limitations

- Ease of starting—must be fully withdrawn from opioids
  - short-acting (6 days)
  - long-acting opioids (7-10 days)
- Not recommended for pregnant women
  - Pregnant women who are physically dependent on opioids should receive treatment using methadone or buprenorphine monoproduct
- Not suitable for patients with liver disease
- Diminished tolerance to opioids, unaware of consequent increased sensitivity to opioids if they stop taking naltrexone

Kampman, K. et al. (2015). *The ASAM National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use*. Retrieved from http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24

Opioid Agonist Therapy
(Methadone and Buprenorphine)



Methadone Hydrochloride

- Full opioid agonist
- Oral - 80-90% oral bioavailability
- Tablets, Liquid Solution, Parenteral (↓50%)
- PO onset of action 30-60 minutes
- Duration of action
  - 24-36 hours to treat opioid use disorders (OUD)
  - 6-8 hours to treat pain
- Proper dosing for OUD
  - 20-40 mg for acute withdrawal
  - > 80 mg for craving, "opioid blockade"

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 clinics

Methadone Maintenance Treatment

Benefits

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

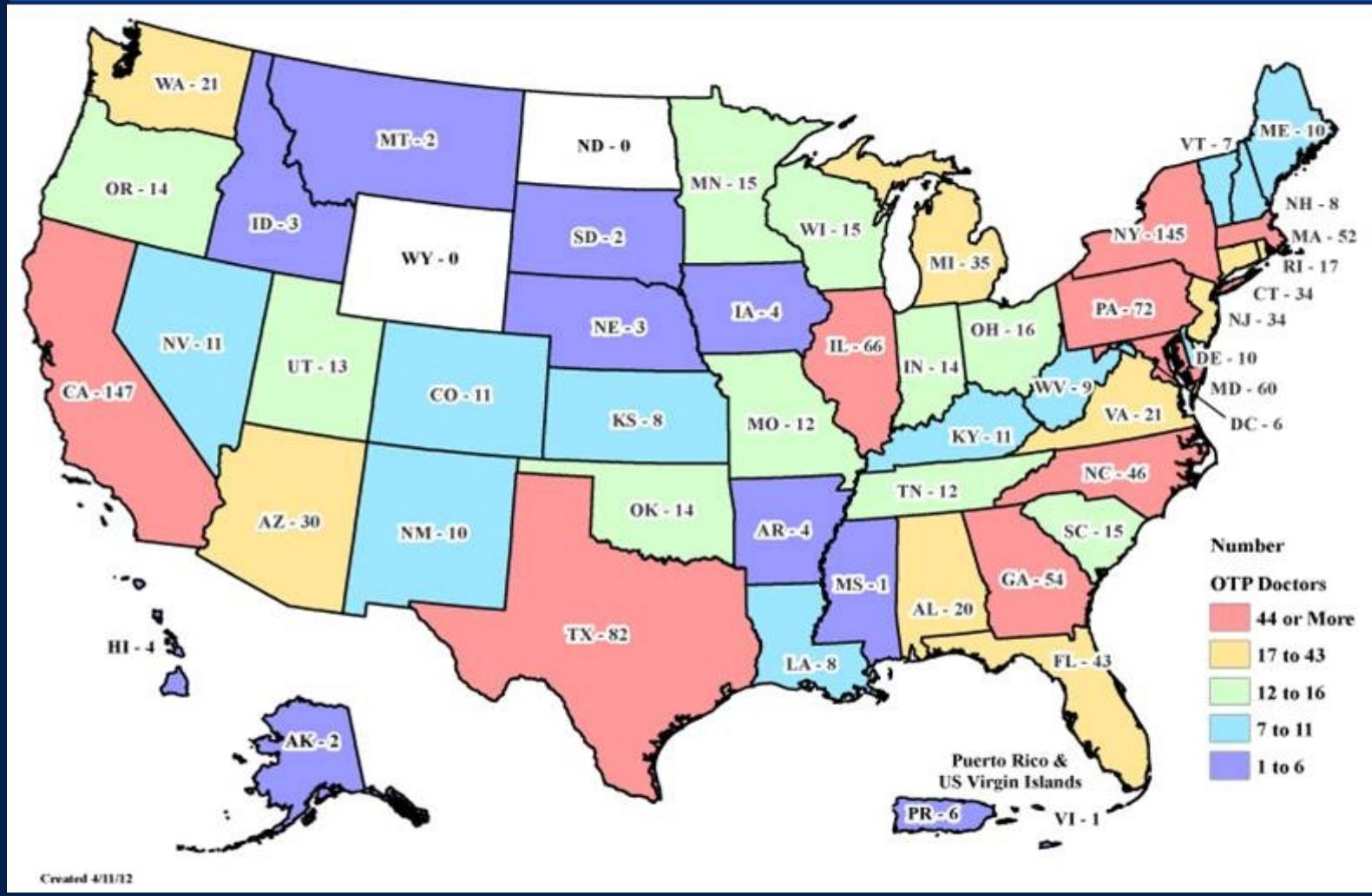
Joseph et al. Methadone Maintenance Treatment: A Review of Historical and Clinical Issues. Mt Sinai J Med. 2000;67:347-364.

Methadone Maintenance Treatment

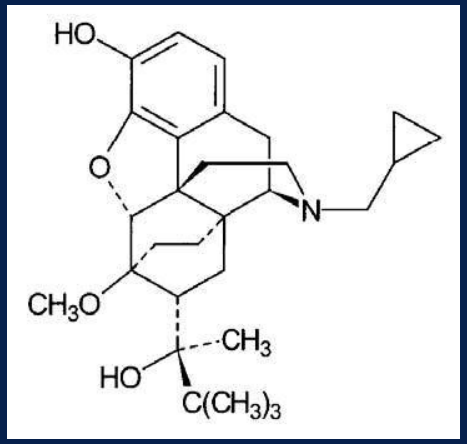
Limitations

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

SAMHSA/Center for Substance Abuse Treatment
Distribution of Opioid Treatment Programs in the United States



Buprenorphine



- Partial mu-opioid agonist , k antagonist
- Schedule III—up to 5 refills

- Metabolism
  - In liver with N-dealkylation by cytochrome P450 3A4 enzyme system into an active metabolite norbuprenorphine
    - Norbuprenophine undergoes further glucuronidation
- Elimination
  - Excreted hepatobiliary (70%) and urine (30%)
    - Mean elimination half-life = 37 hours
  - Commercial screening urine drug test for parent compound.
  - Does NOT show as opiate positive on standard screen

Buprenorphine Formulations FDA Approved for OUD

Sublingual and Buccal forms (tablets and films)

- "Combo" (buprenorphine/naloxone): tablets and films
- "Mono" (buprenorphine): generic tablets

Parenteral

- "Mono" (buprenorphine): implantable rods
- "Mono" (buprenorphine): monthly injection

- Approved for moderate to severe opioid use disorder
- Can be used **OFF LABEL** for pain

Buprenorphine Formulations not FDA Approved for OUD

Parenteral, Transdermal Patches and Buccal Film formulations

- Buprenex®
- Butrans®
- Belbuca®

- Approved for pain but **NOT** OUDs
- **Can NOT be used OFF LABEL** for OUDs: Violates DATA 2000

Purpose of Naloxone in "Combo"

- Naloxone has limited bioavailibility PO or SL, 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 opioid physically dependent.
    - Decreasing diversion and misuse
  - Naloxone will block, or attenuate, the opioid agonist effect of the buprenorphine
  - Therefore safer if diverted

Comer S. *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

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

Buprenorphine Efficacy Summary

- Studies (RCT) show buprenorphine more effective than placebo and equally effective to moderate doses (80 mg) of methadone on primary outcomes of:
  - Abstinence from illicit opioid use
  - Retention in treatment
  - Decreased opioid craving

Johnson et al. *NEJM.* 2000.
Fudala PJ et al. *NEJM.* 2003.
Kakko J et al. *Lancet.* 2003.

Overdose Risk Minimal

- Low risk of clinically significant problems
- Pre-clinical studies suggest high doses of buprenorphine should not produce respiratory depression
- No reports of respiratory depression in clinical trials
- Overdose and misuse (e.g., injecting) of buprenorphine combined with other CNS depressants result in respiratory depression and risk overdose
- France experience…
  - IV buprenorphine + high potency benzodiazepines → deaths

Buprenorphine Safety

- Highly safe medication
  - For both acute and chronic dosing
- Primary side effects:
  - Nausea and constipation
    - Like other mu opioid agonists, but may be less severe and more self-limiting
- No evidence of significant disruption in cognitive or psychomotor performance with buprenorphine maintenance
- No evidence of organ damage with chronic dosing of Buprenorphine "mono" or "combo"

LFTs with Sublingual Buprenorphine

From Package Insert: Cases of cytolytic hepatitis have been observed in clinical trials and post-marketing AE reports. Ranges from transient asymptomatic to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy…

Check LFTs prior for baseline and monitor periodically. Use not recommended in patients with severe hepatic impairment. Hepatic impairment results in reduced clearance of naloxone > then buprenorphine thus interfering with buprenorphine efficacy….

LFTs with Sublingual Buprenorphine

AST and ALT	Bup/nx (n=340) n (%)
Baseline ≤2x ULN remained <2x ULN	273 (80.3)
Baseline ≤2x ULN then increased >2x ULN	43 (12.6)
Baseline >2x ULN then decreased and remained ≤2x ULN	11 (2.4)
Baseline >2x ULN not decrease ≤2x ULN or increase >2x baseline	1 (0.2)
Baseline >2x ULN then increased >2x baseline	9 (2.6)

AJ Saxon et al. *Drug and Alcohol Dependence.* 2013.

LFT Recommendations

Level of Evidence: Moderate

- Obtain LFTs, prothrombin time/INR, hepatitis serologies prior to initiating buprenorphine
- Periodically monitor LFTs. There is no empirical evidence currently to guide the frequency of monitoring. The frequency of monitoring determined by physician discretion but semi-annual frequency appears to be adequate in patients without other risk factors
- If a patient does have clinical and/or laboratory evidence of hepatotoxicity (e.g. transaminases >5X upper limit of normal, abnormal bilirubin or abnormal prothrombin time)
  - All possible causes of liver injury should be evaluated
  - Consideration should be given to lowering the dose of buprenorphine or discontinuing buprenorphine

www.pcssmat.org

Abuse Potential of Buprenorphine

- Euphoria in non-opioid dependent individuals
- Abuse potential less than full opioid agonists
- Abuse among opioid-dependent individuals is relatively low
- Combination product theoretically less likely to be abused by IV route
- Most illicit use is to prevent or treat withdrawal and cravings

Yokel MA et al. *Curr Drug Abuse Rev.* 2011.
Lofwall MR, Walsh SL. *J Addic Med.* 2014.

Module II

Implementing Office-Based Opioid Treatment (OBOT)

Module II Objectives

This module will cover an overview of implementing Office-Based Opioid Treatment (OBOT) including:

- Patient assessment
- Office management
- Medication management
- Role of nonpharmacotherapy
- Patient monitoring
- Relapse
- Case discussion: Induction and Stabilization

Patient Assessment

Assessment Overview

1. Establish diagnosis of opioid use disorder and current opioid use history
2. Document use of alcohol and other drugs and need for medically supervised withdrawal management
3. Identify comorbid medical and psychiatric conditions; how, when, where they will be addressed
4. Screen for and address communicable diseases
5. Evaluate level of physical, psychological and social functioning or impairment
6. Determine patient's readiness to participate in treatment

DSM-5 Opioid Use Disorders[1]

1. Tolerance[2]

2. Withdrawal[2]

Loss of Control

3. Larger amounts and/or longer periods

4. Inability to cut down on or control use

5. Increased time spent obtaining, using or recovering

6. Craving/Compulsion

Use Despite Negative Consequences

7. Role failure, work, home, school

8. Social, interpersonal problems

9. Reducing social, work, recreational activity

10. Physical hazards

11. Physical or psychological harm

[1] Mild (2-3), moderate (4-5), severe (≥6)

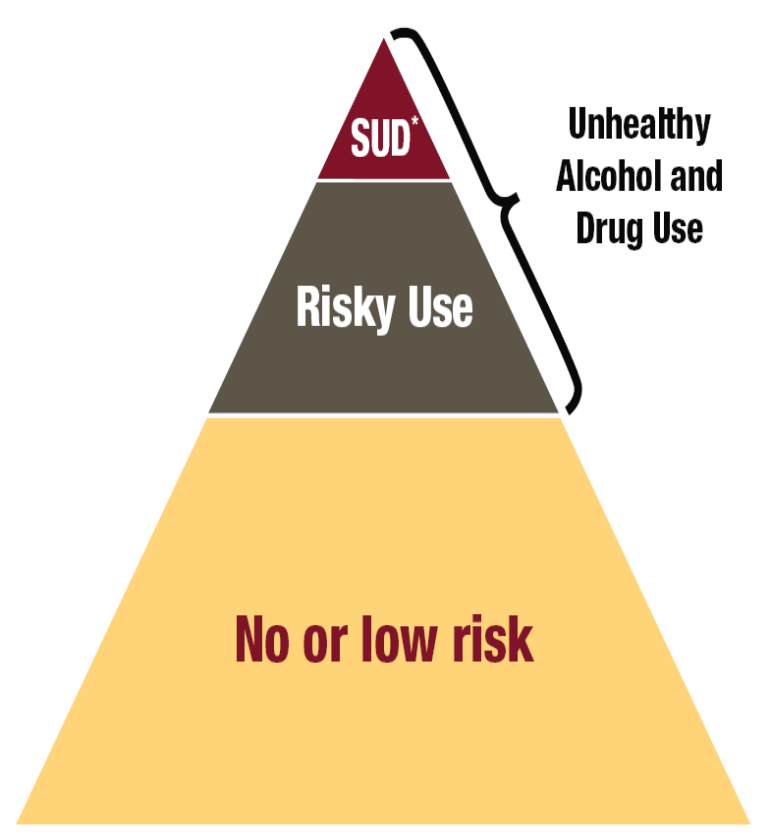
[2] Not valid if opioid taken as prescribed

APA. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.)

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

Screening for Alcohol and Other Substance Use



Alcohol

"Do you sometimes drink beer, wine or other alcoholic beverages?"

"**How many times** in the past year have you had 5 (4 for women) or more drinks in a day?"

(positive: > never)

Drugs

"**How many times** in the past year have you used an illegal drug or used a prescription medication for non-medical reasons?"

(positive: > never)

Smith PC et al. *J Gen Intern Med*. 2009; 24(7):783-8.
Smith PC et al. *Arch Intern Med*. 2010; 170(13):1155-60.
Image source: SBIRT Clinician's Toolkit www.MASBIRT.org

Concurrent sedative-hypnotics?

Alcohol and other sedative-hypnotics are relative contraindications to buprenorphine

- Deaths have resulted from injecting buprenorphine and benzodiazepines
- Avoid alcohol while taking buprenorphine to avoid overdose

Identify and refer patients who are willing and able to undergo medically supervised withdrawal management from alcohol, benzodiazepines, or other sedatives

Fishman et al. 2005; McNicholas, 2008; Lavie et al. 2005.

FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks

This provides updated information to the **FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning (/Drugs/DrugSafety/ucm518473.htm)** issued on August 31, 2016.

Safety Announcement

[9-20-2017] Based on our additional review, the U.S. Food and Drug Administration (FDA) is advising that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce these risks. We are requiring this information to be added to the buprenorphine and methadone drug labels along with detailed recommendations for minimizing the use of medication-assisted treatment (MAT) drugs and benzodiazepines together.

Buprenorphine and methadone help people reduce or stop their abuse of opioids, including prescription pain medications and heroin. Methadone and buprenorphine have been shown to be effective in reducing the negative health effects and deaths associated with opioid addiction and dependency.[1] These medications are often used in combination with **counseling and behavioral therapies (https://www.samhsa.gov/medication-assisted-treatment/treatment#counseling-behavioral-therapies)**, and patients can be treated with them indefinitely. Buprenorphine and methadone work by acting on the same parts of the brain as the opioid that the patient is addicted to. The patient taking the medication as directed generally does not feel high, and withdrawal does not occur. Buprenorphine and methadone also help reduce cravings[2] (see Table 1. List of Buprenorphine and Methadone MAT Drugs).

New Safety Measures Announced for Opioid Analgesics, Prescription Opioid Cough Products, and Benzodiazepines FDA: August 2016

Table 1. The Danger of Combining Opioids And Benzodiazepines

FDA Warning: Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of (opioid) and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate
- Limit dosages and durations to the minimum required
- Follow patients for signs and symptoms of respiratory depression and sedation

Source: US Food and Drug Administration website. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518697.

Co-morbidity?

Medical

- Past and present medical illnesses, 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 (heroin), 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

Office Management

Before getting started…

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

Medical Records Confidentiality

- Specific federal and state regulations govern disclosure of a patient's identity and treatment information
- Confidentiality Statutes relevant to treatment of SUDs:
  - Title 42,Part 2,Code of Federal Regulations [42 CFR Part 2]
    - The logic behind these regulations is that persons with SUDs are more likely to seek and succeed at treatment if they know their need for treatment will not be disclosed unnecessarily
    - Knowledge of these statutes is important for those providing SUD treatment as the rules may apply to their practice

Sample Consent Form
Release of Confidential Information

I, _____ (name of patient),

authorize _____

(name or general designation of program making disclosure)

to disclose to _____

(name or person or organization to which disclosure is made)

the following information:

_____

_____

_____

Sample Consent Form Release of Confidential Information (continued)

The purpose of the disclosure authorized herein is to:

_____

_____

(purpose of disclosure, as specific as possible).

I understand that my records are protected under the Federal regulations governing Confidentiality of Alcohol and Drug Abuse Patient Records, 42 CFR Part 2, and cannot be disclosed without my written consent unless otherwise provided for in the regulations.

Sample Consent Form Release of Confidential Information (continued)

I also understand that I may revoke this consent at any time except to the extent that action has been taken in reliance on it, and that in any event this consent expires automatically as follows:

_____

_____ (specification of date, event, or condition upon which this consent expires)

Signature of patient: _____

Signature of parent, guardian or authorized representative when required: _____

Date: _____

Billing for OBOT

- OBOT is standard medical care: billing procedures are standard
- The ICD-10 Code for opioid dependence is F11.20.
- Physicians billing codes: (CPT) billing codes, accepted by all payers
- No specific Addiction Medicine codes. Same codes as other ambulatory care services

DEA Inspection

- DEA is mandated to protect the public's safety
- DEA is required to ensure that DEA Registrants comply with the Controlled Substance Act and its implementing regulations
  - Inspections (Unannounced/Announced) of buprenorphine waivered physicians maintains the integrity of the inspection process
  - Audit of dispensing records to ensure accountability
  - Verify patient limit (30, 100, 275) compliance

Medication Management

Clinical Uses of Buprenorphine

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

Buprenorphine Induction, Early Stabilization

Overall Goals

- To find the dose of buprenorphine at which the patient:
  - Has no opioid withdrawal symptoms
  - Discontinues or markedly reduces use of other opioids
  - Experiences decreased cravings
  - Has minimal/no side effects

First Patient Appointment

- May involve phone screening by staff or provider to assure that provider can meet patient's needs
- Consultation/Evaluation: Patient not in withdrawal: All therapeutic options discussed: If buprenorphine, then arrangements are made for induction
- Patient in withdrawal or imminent withdrawal: an abbreviated evaluation and emergent induction
- Significant others involved if possible

Buprenorphine Induction

Practical Issues

- Options:
  - Keep a supply of medication in the office for induction administration
    - Must keep the records required by federal and state law for maintaining supplies of controlled substances for administration or dispensing
    - Those records may be audited by the DEA
  - Have the patient fill a prescription for the first day's dose and bring medication to the office for administration
  - Fax prescription to pharmacy then have it delivered
  - Unobserved "home" induction
- Advantages and disadvantages to each approach

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

Corresponding doses of buprenorphine products that contain naloxone			
Buprenorphine and naloxone sublingual tablets, including generic equivalents	*Suboxone*® sublingual films	*Zubsolv*® sublingual tablets	*Bunavail*® buccal films
2 mg buprenorphine / 0.5 mg naloxone	2 mg buprenorphine / 0.5 mg naloxone	1.4 mg buprenorphine / 0.36 mg naloxone	
	4 mg buprenorphine / 1 mg naloxone	2.9 mg buprenorphine / 0.71 mg naloxone	2.1 mg buprenorphine / 0.3 mg naloxone
8 mg buprenorphine / 2 mg naloxone	8 mg buprenorphine / 2 mg naloxone	5.7 mg buprenorphine / 1.4 mg naloxone	4.2 mg buprenorphine / 0.7 mg naloxone
	12 mg buprenorphine / 3 mg naloxone	8.6 mg buprenorphine / 2.1 mg naloxone	6.3 mg buprenorphine / 1 mg naloxone
		11.4 mg buprenorphine / 2.9 mg naloxone	

Adapted from: Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers. Available at: https://www.btodrems.com

*

* Kampman, K. et al. (2015). Appendix II: Bioequivalence Information and Charts. In *The ASAM National Practice Guideline: For the Use of Medications in the Treatment of Addiction Involving Opioid Use*. Retrieved from http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24

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

* Kampman, K. et al. (2015). Appendix II: Bioequivalence Information and Charts. In *The ASAM National Practice Guideline: For the Use of Medications in the Treatment of Addiction Involving Opioid Use*. Retrieved from http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24

Corresponding doses of buprenorphine products that contain naloxone			
Buprenorphine and naloxone sublingual tablets, including generic equivalents	*Suboxone*® sublingual films	*Zubsolv*® sublingual tablets	*Bunavail*® buccal films
2 mg buprenorphine / 0.5 mg naloxone	2 mg buprenorphine / 0.5 mg naloxone	1.4 mg buprenorphine / 0.36 mg naloxone	
	4 mg buprenorphine / 1 mg naloxone	2.9 mg buprenorphine / 0.71 mg naloxone	2.1 mg buprenorphine / 0.3 mg naloxone
8 mg buprenorphine / 2 mg naloxone	8 mg buprenorphine / 2 mg naloxone	5.7 mg buprenorphine / 1.4 mg naloxone	4.2 mg buprenorphine / 0.7 mg naloxone
	12 mg buprenorphine / 3 mg naloxone	8.6 mg buprenorphine / 2.1 mg naloxone	6.3 mg buprenorphine / 1 mg naloxone
		11.4 mg buprenorphine / 2.9 mg naloxone	

Adapted from: Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers. Available at: https://www.btodrems.com

* Kampman, K. et al. (2015). Appendix II: Bioequivalence Information and Charts. In *The ASAM National Practice Guideline: For the Use of Medications in the Treatment of Addiction Involving Opioid Use*. Retrieved from http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24

Buprenorphine Induction

Patient Instructions

- Come to office in mild to moderate withdrawal
- Don't plan to drive home
- Plan to be at clinic or office for up to 3 hours (may bring a sandwich, book, etc.)
- Ready to give urine sample
- Bring medication bottle, or have it delivered if applicable (prescribe vs. dispense)
- Accompanied by significant other, if possible

COWS: Clinical Opioid Withdrawal Scale

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset:** *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____
Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal	

Wesson DR et al.
J Psychoactive Drugs. 2003

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.

Induction – Day 1
Not currently dependent on opioids

- Uncommon
- Can still meet DSM-5 criteria
- No precipitated withdrawal concerns
- Start low (2 mg), and go slow to avoid opioid side effects
- Patients are very good at titrating buprenorphine
- Give them general parameters

Induction – Day 1
Dependent on short-acting opioids

- Instruct patients to abstain from any opioid use for 12-24 hours (so they are in mild withdrawal at time of first buprenorphine dose)

Induction – Day 1
Dependent on short-acting opioids

If patient is not in opioid withdrawal at time of arrival in office:

- Assess time of last use and consider either:
  - Having him/her return another day
  - Waiting in the office until evidence of withdrawal is seen
  - Or leaving office and returning later in day (with strict instructions to not take opioids while away from the office)

Induction – Day 1
Dependent on short-acting opioids

- First dose: 2/0.5-4/1 mg SL buprenorphine/naloxone
  - Monitor in office for 1 hr after first dose and each subsequent dose
  - Relief of opioid withdrawal should begin within 30-45 minutes
- Period of greatest severity of buprenorphine-related precipitated withdrawal occurs in the first few hours (1-4 hours) after a dose

Induction – Day 1
Dependent on short-acting opioids

The length of time the patient is monitored in the office varies depending upon:

- The clinician's familiarity with the patient
- The clinician's familiarity with using buprenorphine
- The patient's level of support at home

Induction – Day 1
Dependent on short-acting opioids

- Can re-dose if needed (every 1-2 hours, if opioid withdrawal subsides then reappears)
- Maximum first day dose of buprenorphine/naloxone= 8mg----16mg
  - Dose equivalent of other formulations; e.g. 5.7—11.4 mg of branded SL tablets

Induction – Day 1
Dependent on long-acting opioids

- Recommendations vary about optimal dose of long-acting opioid for transfer (TIP 40 states <30 mg/d methadone)
  - More recent clinical experience suggests patients should have dose decreases until they are down to <40 mg/d of methadone or the equivalent
- Begin induction at least **48-72** hours after last dose of methadone, and 36 hours after last dose of sustained release oxycodone (or longer)
- Patient should be in mild to moderate withdrawal at time of first buprenorphine dose
- Use similar induction procedures to "dependent on short-acting opioids"

Induction – Day 1
Managing Precipitated Withdrawal

- If a patient has precipitated withdrawal consider
  - Giving another dose of buprenorphine, attempting to provide enough agonist effect from buprenorphine to suppress the withdrawal
  - Stopping the induction, provide symptomatic treatments for the withdrawal symptoms, and have patient return the next day
- Since the latter would risk loss of the patient, the first option should be considered

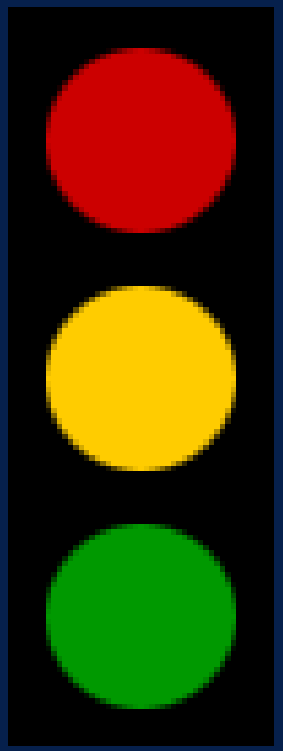
Stabilization/Maintenance

- On 2nd day, be in contact with patient (in office, via phone, etc.)
- Adjust dose accordingly based on patient's experiences on first day
- Continue adjusting dose by 2/0.5-4/1 mg increments until an initial target dose of 8/2—16/4 mg is achieved during the induction phase
- Generally 24mg of buprenorphine is considered a maximal dose, but some patients may require a higher dose

Stabilization/Maintenance

- After the first day of buprenorphine, induction for patients who are dependent on either short-acting or long acting opioids, the procedures are essentially the same
- Adjust dose according to the patient's experiences:
  - Lower dose if patient was over-medicated at end of Day 1
  - Higher dose if there were withdrawal symptoms after leaving your office and/or if patient used opioid agonists
- Don't assume abstinence after the first day's dose

Buprenorphine Dosing



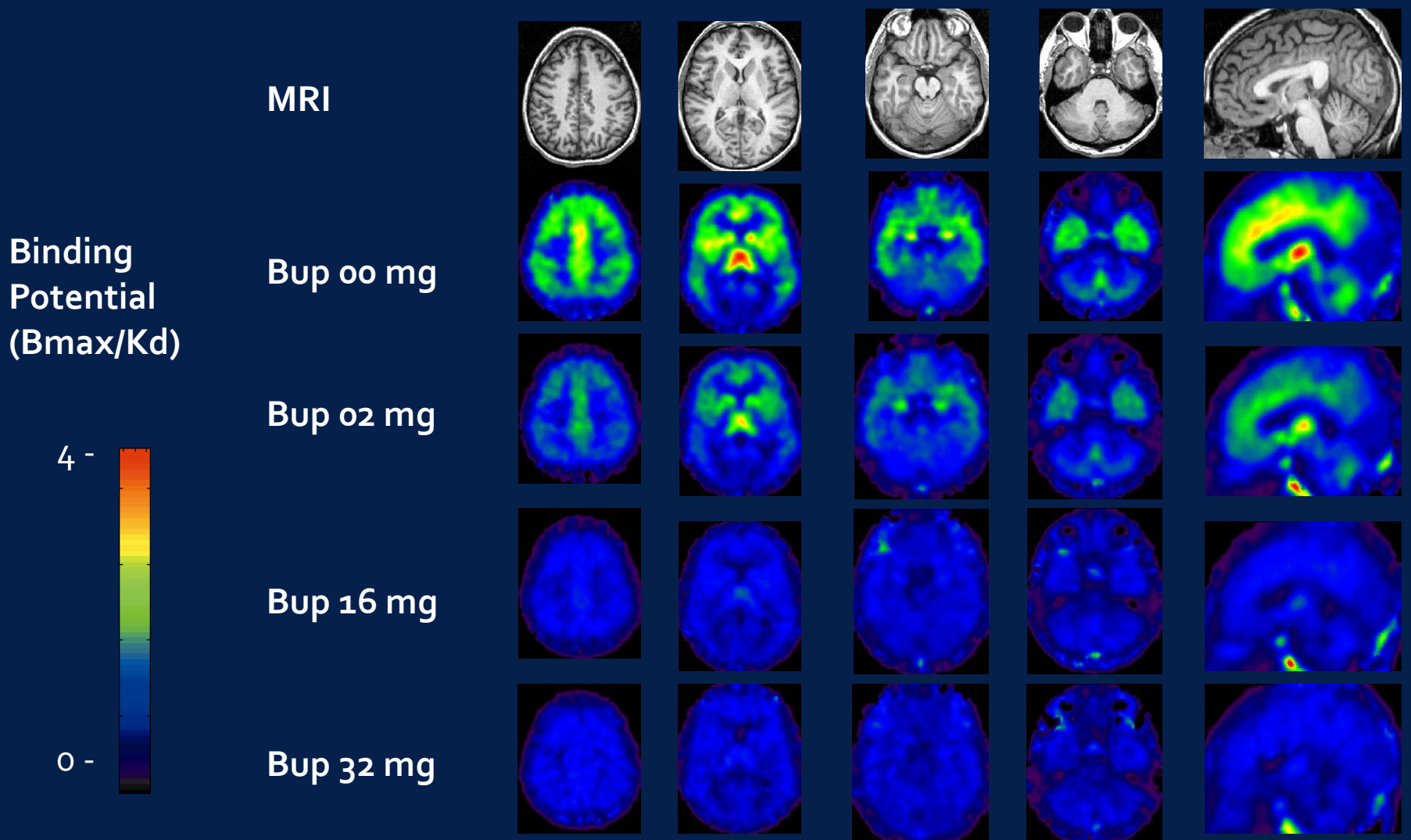
> 24 mg/day (Full Review: medical/behavioral)

> 16–24 mg/day (Consider: Patient Difference)

≤ 16 mg/day (typical)

Zubieta et al., 2000; Greenwald et al. 2003; Product Information Suboxone 2005; personal communication RE Johnson, June, 2007.

Mu Opioid Receptor Blockade



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

Stabilization/Maintenance

- The patient should receive a daily dose until stabilized
- Patient should be dosed once daily or twice daily, but not more frequently than twice daily
- Multiple daily doses which mimic addictive behavior is not recommended
- An exception daily dosing (e.g. 4mg qid) is indicated if concurrent opioid use disorder and pain are being treated.

Stabilization/Maintenance

- Once stabilized, the patient can be shifted to alternate day dosing (e.g., every other day, MWF, or every third day, MTh)
- Increase dose on dosing day by amount not received on other days (e.g., if on 8 mg/d, switch to 16/16/24 mg MWF)
- Non-daily dosing is most appropriate if the patient is receiving observed dosing in an OTP
- For OBOT patients daily dosing is the norm

Bickel WK et al. *Psychopharmacology* 146:111-118, 1999.
Johnson RE et al. *Drug Alcohol Depend*. 40:27-35, 1995.

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)

Buprenorphine Discontinuation

- First question is why?
- Many studies show high relapse rates with tapers and withdrawal from maintenance agonist
- Some studies show normalization of brain function with maintenance
- Comprehensive discussion with patient and significant others to explore reasons for discontinuation

Buprenorphine Discontinuation

- Patients should continue to be followed by provider after discontinuation
- Naltrexone therapy should be considered
- Psychosocial treatments should continue
- Patients should be told they can resume buprenorphine treatment if cravings, lapses, or relapses occur

Medically Supervised Withdrawal Management Using Buprenorphine

- Conflicting data on outcomes comparing shorter versus longer duration of tapering
- Regardless of the buprenorphine withdrawal duration consider use of ancillary medications to assist with symptoms of opioid withdrawal (e.g., medications for arthralgias, nausea, insomnia)

Dunn, K et al. *Drug and Alcohol Dependence*. 2011.
Amass L et al. *Am J Addictions* 13:S42-66, 2004.

Medically Supervised Withdrawal Management Using Buprenorphine

Rapid ≤ 3 days

- Reports show buprenorphine suppresses opioid withdrawal signs and symptoms (better than clonidine)
- Using sublingual tablets:
  - First day: 8/2-12/3 mg sl
  - Second day: 8/2-12/3 mg sl
  - Third (last) day: 6/1.5 mg sl

Cheskin LJ et al. *Drug Alcohol Depend* 36:115-121, 1994.
O'Connor PG et al. *Ann Inter Med* 127:526-530, 1997.

Medically Supervised Withdrawal Management Using Buprenorphine

30 days*

Study Day	Buprenorphine-Naloxone Dose mg
1	4 + additional 4 as needed
2	8
3	16
4	14
5	12
6	10
7	8
8	6
9	4
10	2
11	2

Withdrawal over 4-30 days is common in clinical practice. Buprenorphine is very flexible and withdrawal can be achieved rapidly or slowly, depending on treatment issues.

*Protocol Developed by NIDA Clinical Trials Network

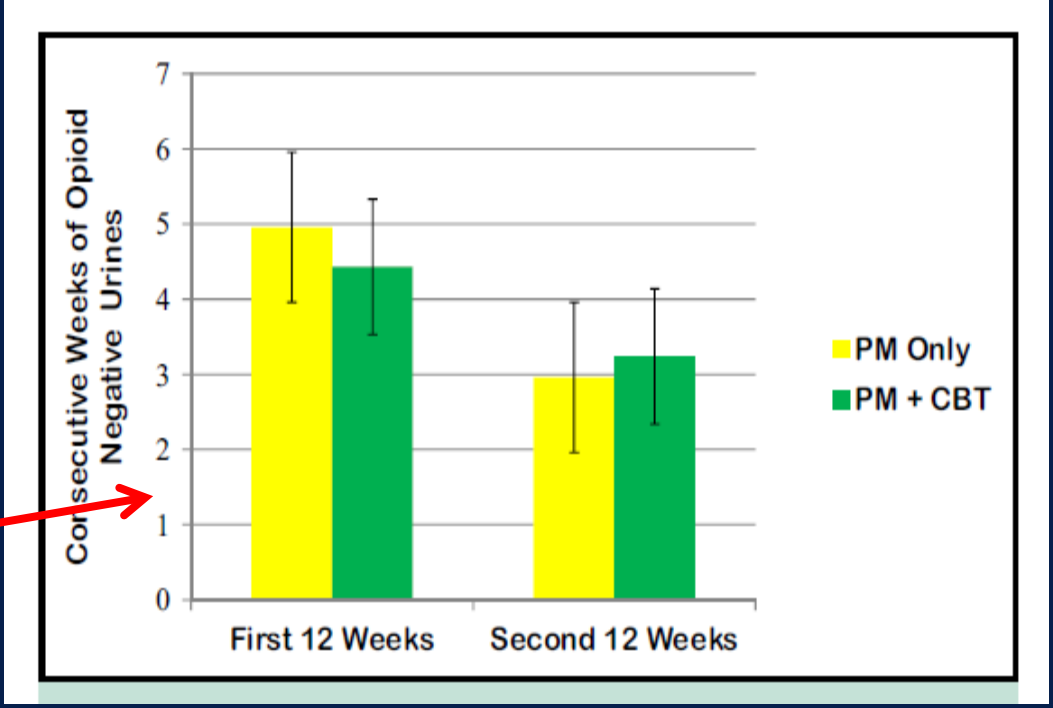
Role of Non-Pharmacological Treatment

Opioid Use Disorder (OUD): Behavioral Treatment Components

- Psychosocial Services: often helpful for treatment of OUD
  - Can be delivered directly by physician and/or by referral when needed
- DATA 2000: "…the practitioner has the capacity to refer the patients for appropriate counseling and other appropriate ancillary services."
- Refer patient as clinically determined to:
  - Individual and group therapy
  - Family therapy
  - 12 Step
  - Higher psychiatric severity patients more responsive to increased services

Is Behavioral Treatment in OBOT Effective?

- Three trials show that additional behavioral therapy (i.e., CBT, drug counseling) does NOT significantly improve outcomes over that achieved by buprenorphine PLUS medical management or "medical counseling"



Weiss RD et al. *Arch Gen Psychiatry.* 2011.
Fiellin DA et al. *Am J Med.* 2013.
Ling W et al. *Addiction*. 2013.

Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence (WHO 2009)

Recommendation

Psychosocial support should be offered routinely in association with pharmacological treatment for opioid dependence.

- Strength of recommendation – strong
- Quality of evidence – high
- Remarks – While patients should be offered psychosocial support, they should not be denied agonist maintenance treatment should they refuse such support.

Treatment services should aim to offer onsite, integrated, comprehensive psychosocial support to every patient. However, treatment services should not deny effective medication if they are unable to provide psychosocial assistance, or if patients refuse it.

Primary Care Medical Management
Critical Elements

- Provision of buprenorphine maintenance
- Monitoring of compliance with buprenorphine maintenance
- Monitoring of patients' drug use, symptoms, and progress
- Education regarding opioid use disorder and buprenorphine maintenance treatment
- Encouragement to achieve abstinence from illicit opioids and to adhere to all treatment recommendations
- Encouragement to attend self-help groups
- Provision of brief advice modeled on the education provided in standard drug counseling, such as encouraging patients to make lifestyle changes that support recovery, and to avoid potential triggers of drug use
- Identification and treatment of medical complications of opioid use
- Referrals to specialty services in the community (e.g., vocational, legal, housing or social services) if necessary

Patient Management, Monitoring

Monitoring Treatment Goals

- Discuss and document specific goals
- Set specific time periods
- Document progress on goals at each visit
- Examples:
  - Achieve abstinence from illicit and non-prescribed drugs
  - Meet with clinician
  - Attend meetings
  - Job applications

Follow-up Visits

- Face-to-face visits to check safety, adherence
- Initial Frequency: every 1-2 weeks until stable
  - Monthly once stabilized
- Check dosing, intervals, sublingual technique
- Safety issues: side effects, safe storage

Follow-up Visits

- Withdrawal/craving/triggers
- Tobacco, alcohol, and other drug use
- Urine drug tests (UDT) and pill counts
  - Frequency varies with treatment stage
- Prescription drug monitoring program (PDMP)

Follow-up Visits

- Confirm behavioral treatment
- Medical problems & symptoms
- Psychiatric problems & symptoms
- Outside medications and providers
- Housing
- Employment
- Family/Relationships
- Legal issues

Urine Drug Testing (UDT)

- Objective information
  - Evidence of therapeutic adherence
  - Evidence of use or non-use of illicit drugs
- Monitoring of treatment progress and safety
- Reinforces success with treatment
- Part of standard of care
- Identify those who may need higher level of care

UDT: Frequency

- SAMHSA TIP 40 2004
  - At least monthly
  - More frequently early in treatment (every 1-2 weeks)
- Vary among states, insurers
- Urine is preferred medium for testing due to
  - Ease of obtaining sample
  - Presence, persistence of metabolites
  - Lowest cost
  - Availability of office-based testing tools

UDT: Implementation

- Discuss with patient
  - This is for safety and is the standard of care
- Know scope and limits of tests and lab
  - ***Beware*** false negatives and positives
- Consider random versus scheduled testing
- Incorporate quality control procedures
- Consider establishing consult lab linkage
  - GCMS/LCMS confirmatory testing
  - Expert consultation on test interpretation
  - Online reporting of results
  - Onsite and/or observed testing when needed

UDT: Immunoassays

PROS

- Point of care, or lab based
- Fast
- Easy
- Cheap
- Specific tests available for many drugs
  - Oxycodone
  - Buprenorphine
- Can be used as screening with option for confirmation

CONS

- Qualitative tests
  - cutoff ng/ml
    - Opiates: 300
    - Cocaine metabolite: 300
- False positives
  - Cross-reactivity
  - Contamination
- No non-morphine opioids
  - Unless specifically tested
- No non-oxazepam benzos
  - Unless specifically test

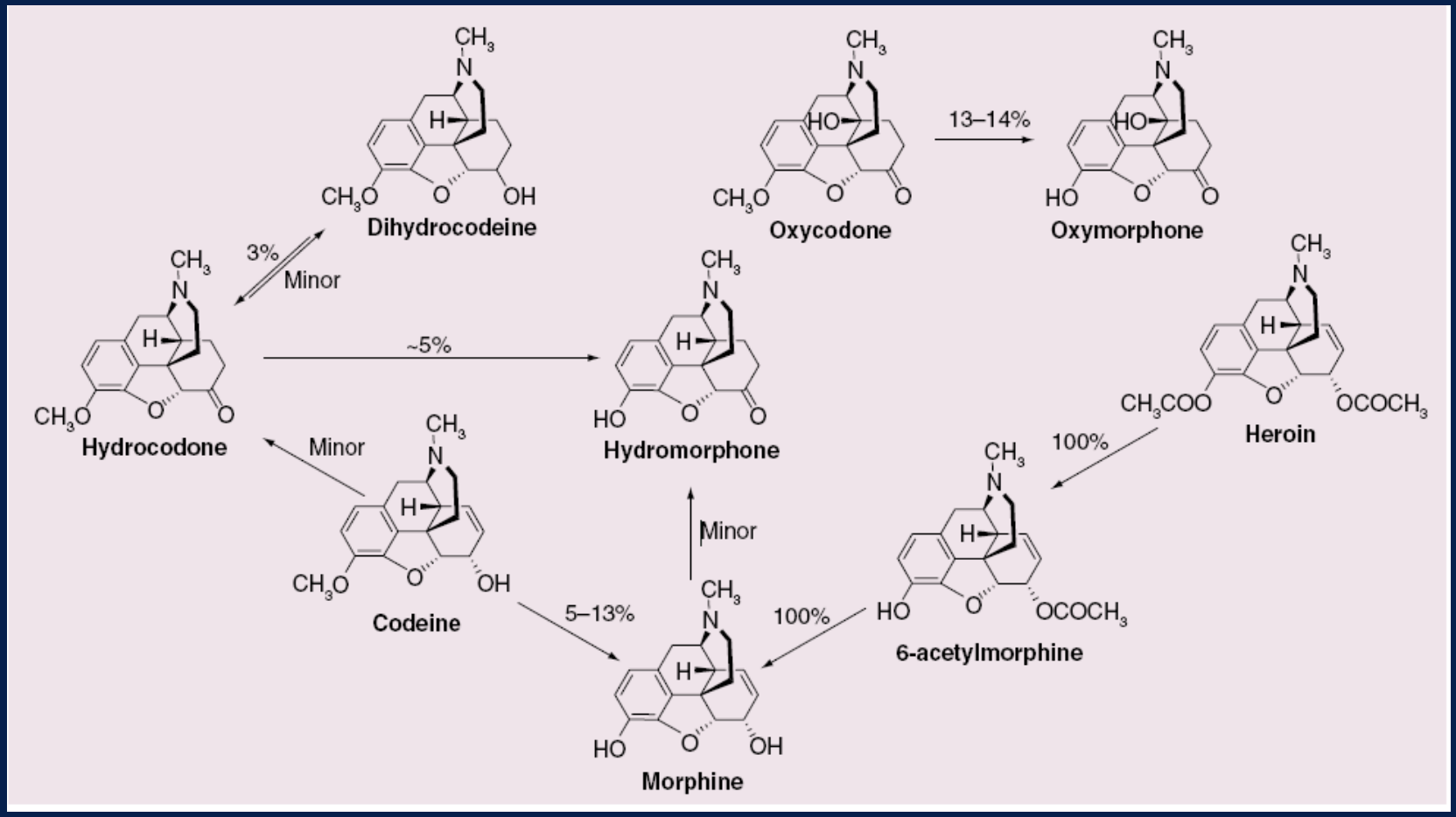
UDT: Detection Windows in Urine

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

UDT: GCMS/LCMS

- Gas or liquid chromatography, mass spectrometry
- Quantitative
- Limitations
  - More costly
  - Requires specialized lab
  - Levels do not indicate amount of medication taken!
    - Variables: time of dosing, metabolism, GFR, hydration

UDT: Opioid Metabolism



Reisfield GM et al. *Bioanalysis.* 2009;1(5):937-52.

Pill Counts

- Objective information
  - Confirm medication adherence
  - Minimize diversion
- Frequency varies with patient progress
- Best option when diversion suspected
- Patient brings in medication supply
- Confirm patient ID and fill date on bottle/box
- Have patient count them in front of staff member
- All tablets should be identical
- Amount should match expected quantity

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

PDMP: Limitations

- Methadone and Buprenorphine dispensed from OTPs **not listed** on PDMPs
- VA Health System now listed
- Not all data readily available to providers
- Lack of communication between all state programs
- Time needed to access reports
- Limitations in who can access reports
- Mandatory vs voluntary use of PDMP

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 lessions
- 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.

Break

Case: Induction and Maintenance

Paula

- Mother calls your office seeking treatment for her daughter, Paula, who is addicted to heroin
- Paula is a 23 yo female, graduate student in social work
- She is agreeable to having her mother come in for the consultation and evaluation
- She is comfortable and not in opioid withdrawal during the initial consultation

Paula

- You take a history from Paula while her mother sits in the waiting room
- She relates feeling anxious most of her life.
- She started smoking marijuana and drinking alcohol on the weekends in high school.
- In college she fractured her ankle playing basketball, and was treated with oxycodone. She noticed that in addition to pain control, her anxiety decreased, and she reported feeling "normal" and "peaceful"

Paula

- She continued requesting oxycodone refills even though her pain had resolved
- When the orthopedist refused to continue prescribing oxycodone she started buying them from friends increasing to ~200mg daily
- A year ago she entered a 28 day abstinence-based rehab, never followed up in after care, relapsed 6 weeks later
- Due to cost and availability she switched from oxycodone to sniffing heroin ~10 bags daily—last use 4 hours ago
- Patient agrees to have mother present to discuss treatment options

Paula

- You present the options of opioid agonist maintenance therapy (methadone, buprenorphine), antagonist maintenance with naltrexone, and another attempt at withdrawal management and medication-free treatment
- Paula and her mother have done their research, Paula has a friend doing well on buprenorphine, and they decide on buprenorphine
- They understand that some form of counseling will also be a part of the treatment plan
- Paula has insurance, so access is not a problem

Case Questions

- *Is Paula ready for buprenorphine induction at this time? If not, how will you decide when she is ready?*
- *Is the patient a candidate for unobserved "home" induction?*

Paula

- You explain that since Paula is physically dependent on opioids, she must be in mild-moderate spontaneous withdrawal, to avoid precipitated withdrawal. She has done her homework, and understands the issue
- You tell her to discontinue **all** opioids for at least 12 hours. She has decided on doing the induction the next morning

Paula

- She returns the next day with her mother. She is visibly uncomfortable, and has a COWS score of 12
  - *Is she ready for the induction?*
- You instruct her that buprenorphine/naloxone is always administered sublingually or via the buccal mucosa—never swallowed whole
- She is instructed on the proper administration procedures to maximize buprenorphine bioavailability

Paula

- You give her buprenorphine 4/1 mg
  - *How long to initial effect?*
  - *How long to peak effect?*
- After her initial dose you give her another 4/1 mg for continue withdrawal
  - *When can the patient leave the office?*
- *Can she take more buprenorphine after leaving the office?*
- *When should she contact you?*

Paula

- *Should the stabilization dose be divided or taken once per day?*
- *How often should stabilization doses be increased?*
- *Once dose stabilization occurs, are maintenance dose increases due to tolerance common? Or are lower doses required over time?*

Paula

- Paula remained on buprenorphine/naloxone 16/4 mg per day for the next 6 months and had no relapses.
- She was adherent with weekly counseling and office monitoring including urine drug tests and pill counts.
- There were no concerning behaviors on the PDMP.

Case Questions

- *How long should Paula be maintained on the buprenorphine?*
- *How will you decide if and when she is ready to be tapered?*
- *How would you taper her off buprenorphine?*

Module III

Special Populations
A Brief Review

In this module we will review:

- Adolescents and young adults
- Pregnancy, neonatal abstinence and breastfeeding
- Medical co-morbidities
- Psychiatric co-morbidities
- Managing pain

Adolescents and Young Adults

Use of Pharmacologic Treatment with Adolescents

Pharmacologic therapy is recommended for all adolescents with severe opioid use disorder

- Buprenorphine is considered first line treatment
  - Most methadone clinics cannot admit patients under 18 years old, though methadone may be a good option for young adults with unstable living arrangements as daily visits provide structure and eliminate the need to manage medications at home
  - Naltrexone is also an option for adolescents and also may be clinically useful for adolescents/young adults living away from home, or patients with co-occurring alcohol use disorders

Treatment Duration

The optimal length of time for medication treatment is not known

- Studies in adults have found that patients continued to improve over the course of the first 6 years of treatment
- **However, the impact of exposure to long term agonists/antagonists on the developing brain are unknown**

Confidentiality

Teens Presenting with Parents

- In many cases, adolescents will present for treatment with the knowledge, and often with the support of parents
  - Parents are often the first ones teens turn to for help
- In these cases, managing confidentiality is a clinical decision of what information to share with parents in the context of parents already being aware of the "big picture"

Confidentiality

Teens Presenting Without Parents

- Teens may present for treatment without the knowledge or consent of their parents
- In most states adolescents above a certain age may consent for treatment for an SUD without their parents, though details vary

Confidentiality

Managing Teens That Refuse to Involve Parents

- Ask adolescent their reasons for excluding parents. Many teens could benefit from the support of parents, but are too embarrassed to discuss the problem
- In these cases, offer to treat confidentially and leave the decision of how to proceed up to the teen
- Ask what would happen if a parent learned about a drug problem by accident
- Offer to help "break the news" to parents
- Emphasize that teens who enter treatment should be proud of their decision to get help

Pregnancy
Neonatal Abstinence
Breastfeeding

Pregnancy: Initial Evaluation

- Know about specialized treatment services available in the community for pregnant, opioid-dependent patients
  - Referral should be made regardless of the patient's decision to continue the pregnancy
- Obtain consent to talk to her obstetric provider

Should Women Undergo Withdrawal Management in Pregnancy?

- Initial studies from 1970s demonstrated fetal distress and 5 fold increase in still birth rates with antepartum withdrawal management (Zuspan et al. 1975; Rementeria et al. 1973.)
- More recent data shows 2nd trimester withdrawal management can be safe for the fetus however maternal relapse rates prior to delivery range from 70-98% (Luty et al. 2003; Maas et al. 1990; Dashe et al. 1998.)
- Maintenance therapy in pregnancy has been shown to increase retention in prenatal care, addiction recovery and in-hospital deliveries (Jones et al. 2008.)

Pregnancy: Benefits of Opioid Agonist Therapy

Maternal Benefits

- 70% reduction in overdose related deaths
- Decrease in risk of HIV, HBV, HCV
- Increased engagement in prenatal care and recovery treatment

Fetal Benefits

- Reduces fluctuations in maternal opioid levels; reducing fetal stress
- Decrease in intrauterine fetal demise
- Decrease in intrauterine growth restriction
- Decrease in preterm delivery

Pregnancy: Maintenance Therapy Remains the Standard of Care

- Methadone and buprenorphine (both category C) are safe and effective treatment options in pregnancy
- The decision of which therapy to start is complex and should be individualized for each woman
  - Based on available options, patient preference, patients' previous treatment experiences, disease severity, social supports, and intensity of treatment needed

Fischer et al. 1998, 1999.
Jones et al. 2010.

Management of Buprenorphine Patient: Newly Pregnant

- For women stable on buprenorphine/naloxone who become pregnant:
  - Current standard of care is to switch to **buprenorphine monotherapy at the same dose**
    - The combination therapy has been avoided due to the unknown exposure risk of naloxone in pregnancy (although pregnancy category B) and concern for misuse causing acute withdrawal and fetal distress

Wieggland SL et al. 2015.

Maintenance Therapy in Pregnancy: Neonatal Abstinence Syndrome (NAS)

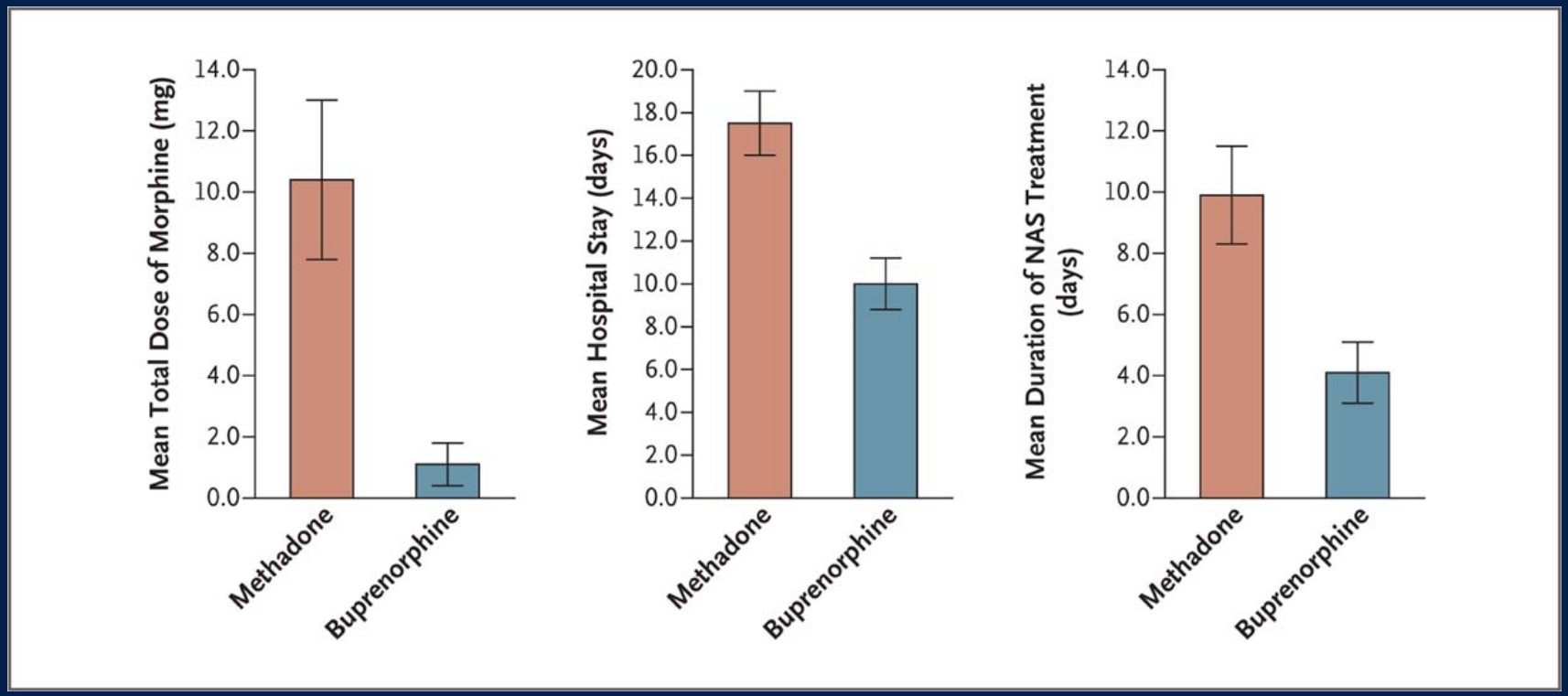
- Generalized disorder with dysfunction of the autonomic nervous system, GI tract and respiratory system
- Occurs in 60-80% of infants with intrauterine exposure to opioid maintenance therapy
- Onset: majority present within 72 hours after delivery
- Duration: up to 4 weeks (prolonged if exposed in-utero to more than one substance associated with NAS)

Maintenance Therapy in Pregnancy: Neonatal Abstinence Syndrome (NAS)

- Meta-analysis of 12 studies from 1996-2012: showed buprenorphine exposed neonates (515) compared to methadone exposed (855) had
  - Shorter mean length of hospital stay (-7.23 days, 95% CI: -10.64, -3.83)
- In treated neonates, buprenorphine exposed
  - Shorter NAS treatment duration(-8.46 days, 95% CI: -14.48, -2.44)
  - Lower morphine dose (-3.60 mg, 95% CI: -7.26, 0.07)

Brogly et al. 2014.

Mean Neonatal Morphine Dose, Length of Neonatal Hospital Stay, and Duration of Treatment for Neonatal Abstinence Syndrome



Jones HE et al. N Engl J Med 2010;363:2320-2331

Maternal Dose and NAS Severity

- No correlation between maternal opioid maintenance therapy dose and the duration or severity of NAS
- Women should be encouraged to report any symptoms of withdrawal through her pregnancy without fear a dose increase will affect her baby's hospital stay or need for NAS treatment

Berghella et al. 2003; McCarthy et al. 2005; Cleary et al. 2010; Isemann et al. 2010; Jones et al. 2010; Seligman et al. 2011.

Opioid Use Disorder and Breastfeeding

- The transfer of methadone and into human milk is minimal and unrelated to maternal doses
- Buprenorphine has poor oral bioavailability and is also compatible with breastfeeding
  - The amount of buprenorphine in human milk is small and unlikely to have negative effects on the infant
- Both are considered Category L3 (probably compatible)

McCarthy JJ 2000; Begg EJ 2001; Jansson LM 2007 & 2008; Hale 2008; Grimm 2005; Lindemalm 2008; Ilett 2012.

Breastfeeding and NAS

- Benefits of breastfeeding for newborns with NAS
  - 30% decrease the development of NAS
  - 50% decrease in neonatal hospital stay
  - Improved mother-infant bonding
  - Positive reinforcement for maternal recovery

Pritham UA et al. *J Obstet Gynecol Neonatal Nurs.* 2012.
Welle-Strand GK et al. *Acta Paediatr*. 2013.
Wachman EM et al. *JAMA.* 2013.
Abdel-Latif ME et al. *Pediatrics*. 2006.

Medical Co-Morbidities

Background

- Persons with opioid use disorders frequently have or at risk of other comorbid medical conditions
- Office-based buprenorphine treatment provides an opportunity to combine substance use treatment with medical care

Non-Occupational Post-Exposure Prophylaxis (nPEP)

- **HIV**: 3-drug ART given<72 hrs after exposure to blood or other potentially infectious body fluids from a known HIV+ or high risk source
- **HBV**: recombinant vaccine series; HBIG within 7 days of unknown or known HBsAg+ source
- **HCV**: no PEP, but curative early treatment

Free expert consultation at national PEPLine: (888) 448-4911

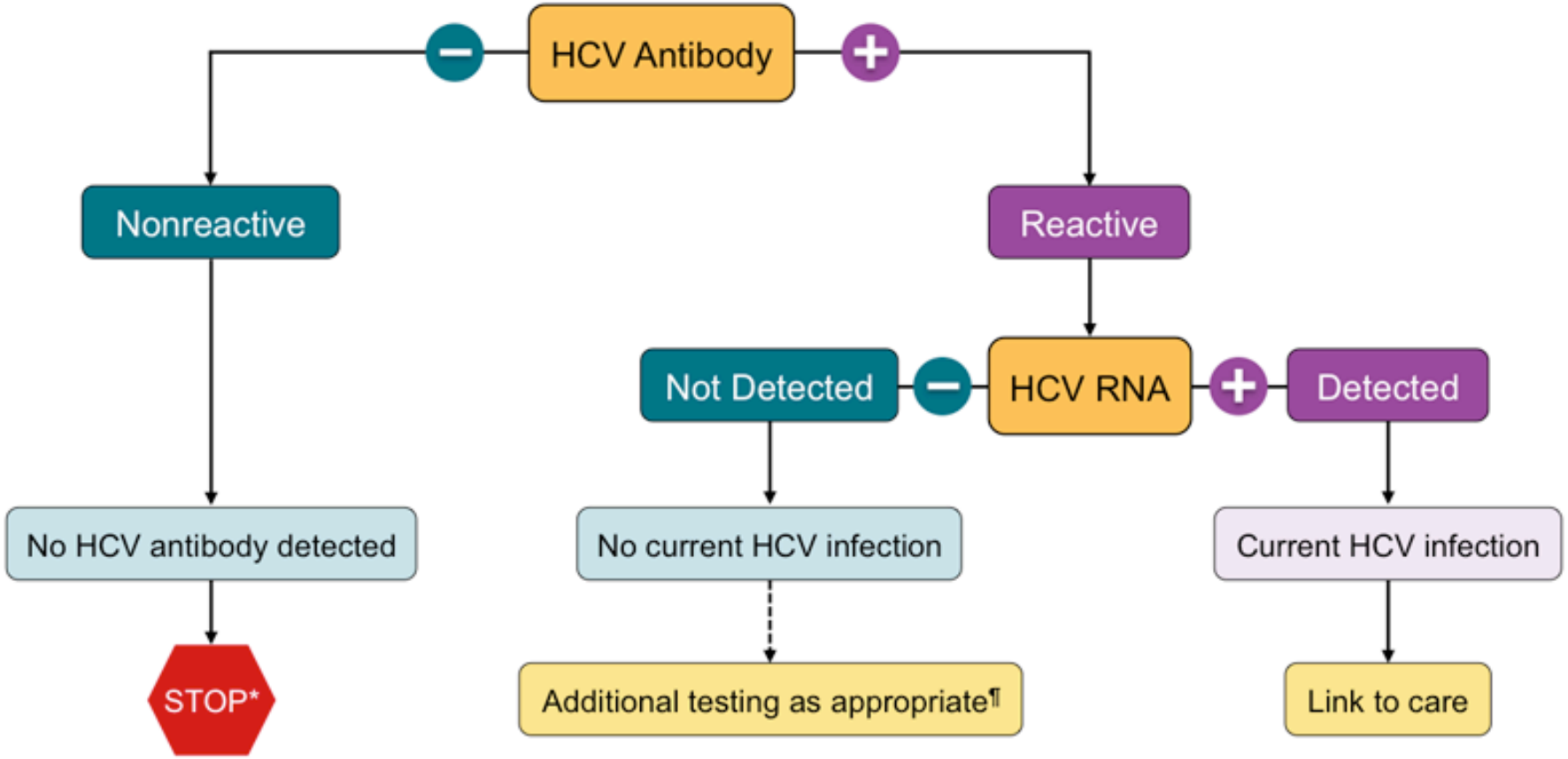
Source: www.cdc.gov/mmwr

Hepatitis C virus infection

The silent epidemic

- Most common blood-borne infection in U.S., 3.2 million people
  - 70-90% PWID; ~30% <age 30
- 40-60% of chronic liver disease
  - Leading indication for liver transplantation
- HCV-related deaths outnumber deaths due to HIV

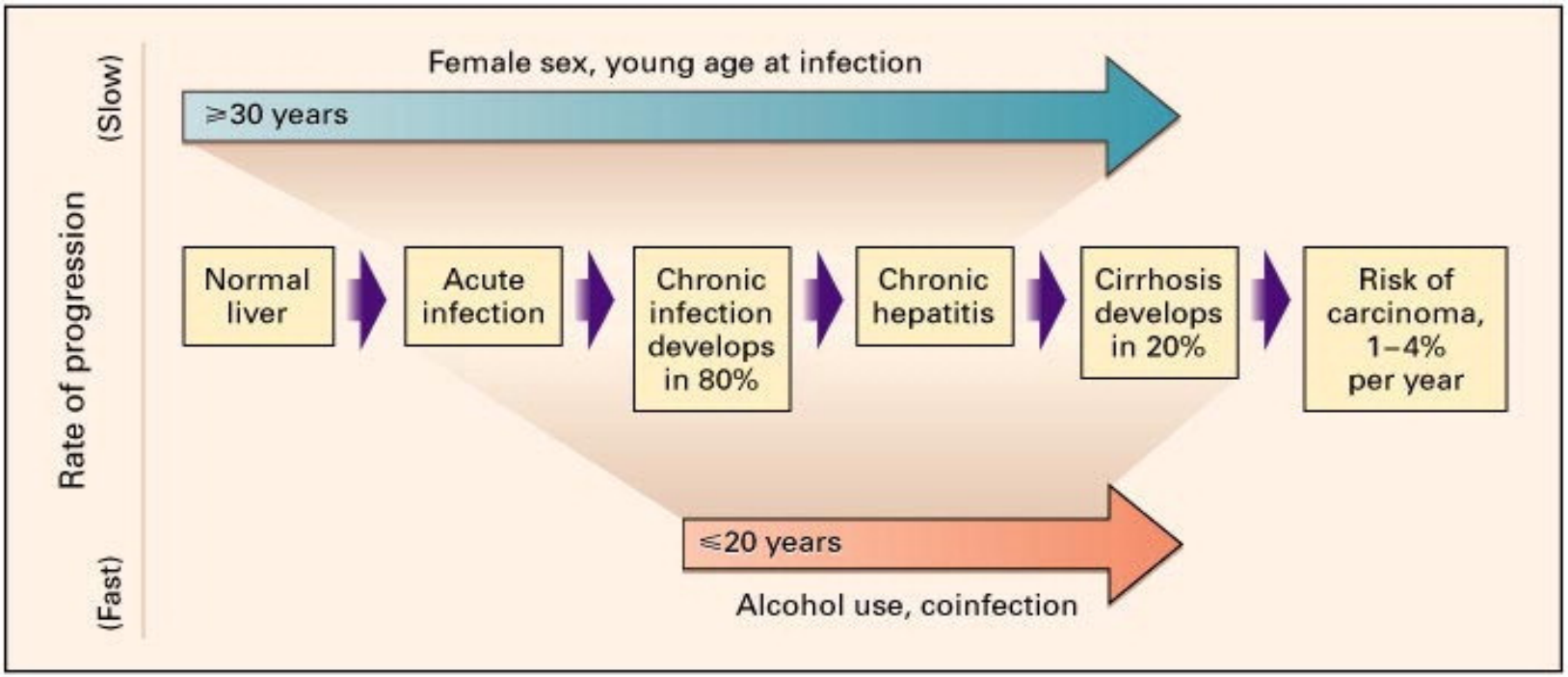
Recommended Testing Sequence for Identifying Current HCV Infection



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

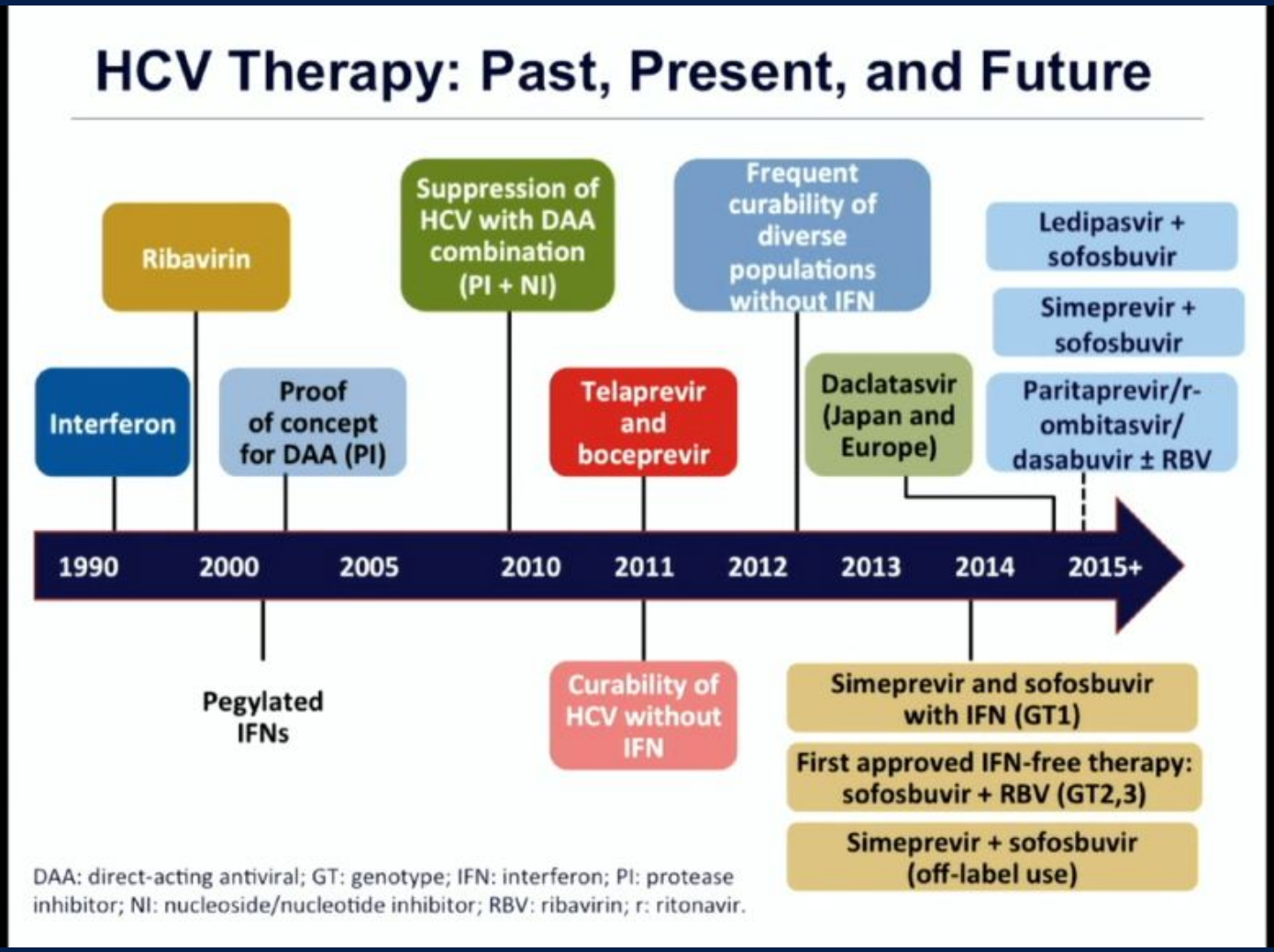
¶To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Natural history of HCV infection, variability from person to person



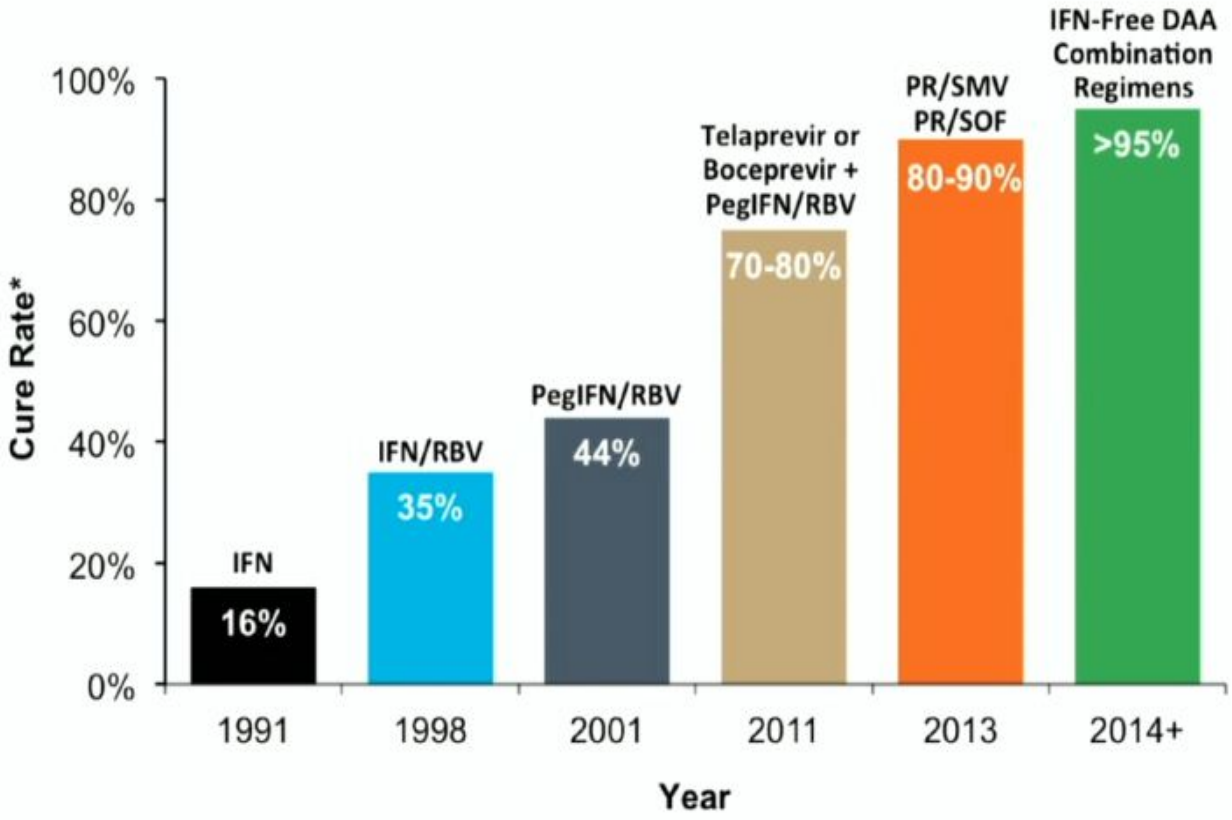
Lauer GM, Walker BD. *N Engl J Med.* 2001; 345:41-52.

The NEW ENGLAND JOURNAL of MEDICINE



CM Rice. Conference on Retroviruses and Opportunistic Infections, Seattle, February 23, 2015.

Rising Cure Rates for Chronic HCV (G1)



CM Rice. Conference on Retroviruses and Opportunistic Infections, Seattle, February 23, 2015.

HIV Treatment

Today's combination antiretroviral therapy: less toxic, fewer pills, higher genetic barrier to resistance

Goals of HIV care:

- Improve individual health outcomes
- Restore health, prolong life in a manner indistinguishable from uninfected persons
- Lower community viral load and HIV transmission to achieve an "AIDS-free generation"

Buprenorphine and HIV Outcomes

HIV-infected patients treated with office-based bup/nx in the Buprenorphine-HIV Evaluation and Support (BHIVES) national demonstration project:

- Decreased opioid use
- Increased HIV ART use
- Experienced higher quality of HIV care
- Reported better quality of life

Altice, Frederick L. et al. *J Acquir Immune Defic Syndr*. 2011;56 Suppl: S22

Psychiatric Co-Morbidities

Induced vs Independent Disorder

- Distinguish between substance-induced disorders versus independent psychiatric disorders
  - Substance-induced: Disorders related to the use of psychoactive substance; typically resolve with sustained abstinence
  - Independent: Disorders which arise during times of abstinence; use of psychoactive substances not the etiology

Substance-Induced Psychiatric Disorders

- Patient's history suggests symptoms occur only when he/she is actively using substances
- Symptoms are related to intoxication, withdrawal, or ongoing neurobiologic perturbation from substances
- Onset and/or offset of symptoms are preceded by increases or decreases in substance use
- Goal should be sustained abstinence followed by re-evaluation of symptoms

Substance-Independent Psychiatric Disorders

- Earliest psychiatric symptoms often precede onset of substance use disorder
- Patient's history suggests symptoms occur during periods when not using psychoactive substances
- May also find a family history of the disorder
- Goal of substance use disorder treatment should still be cessation of substance use, but treatment must also address psychiatric symptoms simultaneously

General Treatment Principles

- Patients with opioid use disorder and independent depressive, anxiety, or stress disorders
  - Can respond to medication and/or psychotherapy treatments for depression, anxiety, and PTSD
  - Anxiety disorders and PTSD typically treated with antidepressants
- Generally avoid use of benzodiazepines
  - Risk of misuse
  - Possibility of interactions with buprenorphine

Buprenorphine and Benzodiazepines:

- Among 34 reported buprenorphine-associated overdoses in France, 31 also had benzodiazepines
- Risks of benzodiazepines
  - Tolerance and withdrawal
  - Excess sedation and falls
  - Cognitive impairment
  - Reinforcement/reward/addiction
- Advantages of benzodiazepines
  - Rapid elimination of anxiety symptoms or insomnia when used short term

Pirnay et al. *Addiction*. 2004.

Managing Pain

Altered Pain Experience

- In experimental pain studies…
  - Patients with active opioid use disorder have less pain tolerance than peers in remission or matched controls
  - Patients with a h/o opioid use disorder have less pain tolerance than siblings without an addiction history
  - Patients on opioid maintenance treatment (i.e. methadone, buprenorphine) have less pain tolerance then matched controls
- Which came first?
  - Opioid use disorder or less pain tolerance?

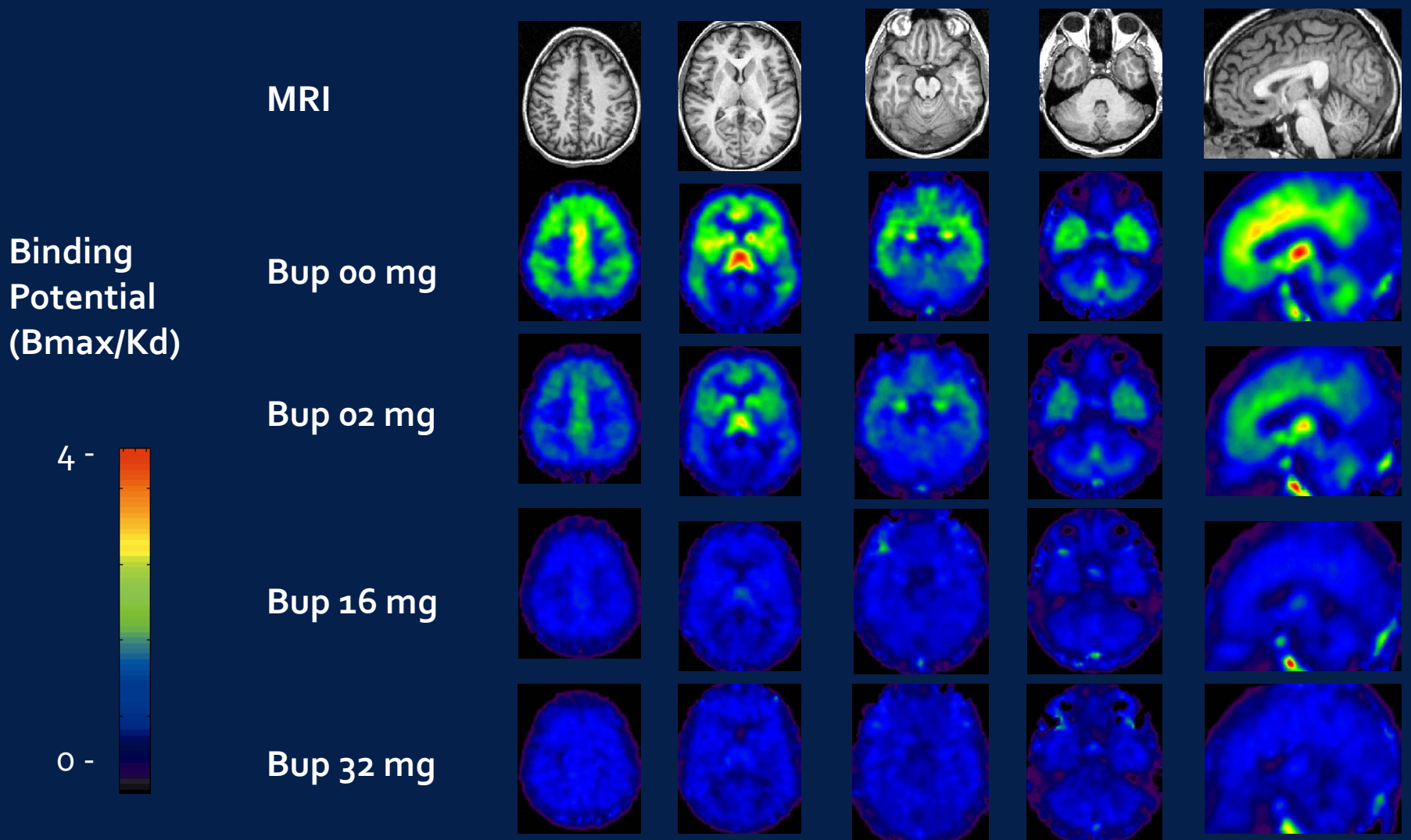
Martin, J 1965; Ho and Dole, V 1979; Compton, P 1994, 2001.

"Opioid Debt"

- Patients with an opioid use disorder who are physically dependent on Opioid Agonist Treatment (i.e. methadone or buprenorphine) must be maintained on a daily equivalence before ANY analgesic effect is realized with opioids used to treat acute pain
- Opioid analgesic requirements are often higher due to increased pain sensitivity and opioid cross tolerance

Peng, PW; Tumber, PS; Gourlay, D. *Can J Anaesthesia.* 2005.
Alford, DP; Compton, P; Samet, JH. *Ann Intern Med.* 2006.

Mu Opioid Receptor Blockade



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

Acute Pain

Buprenorphine Maintenance Treatment

Theoretical Concern

- May antagonize effects of previously administered opioids
- May block the effects of subsequent administered opioids
- However…Experimental mouse and rat pain models
  - Combination of buprenorphine and full opioid agonists (morphine, oxycodone, hydromorphone, fentanyl) resulted in additive or synergistic effects
  - Receptor occupancy by buprenorphine does not appear to cause impairment of mu-opioid receptor accessibility

Kogel, B et al. *European J of Pain*. 2005.
Englberger, W et al. *European J of Pharm*. 2006.

Buprenorphine Maintenance Treatment Options: Acute Pain

- Continue buprenorphine and titrate short-acting opioid analgesic
- D/C buprenorphine, use opioid analgesic, then re-induce
- Divide buprenorphine to every 6-8 hours
- Use supplemental doses of buprenorphine
- Pre-Op; Emerging evidence supports continuing maintenance doses of buprenorphine or methadone, and using IR full agonist opioid analgesics, and/or other analgesic interventions

Alford, DP. *Handbook of Office-Based Buprenorphine Treatment of Opioid Dependence*. 2010.
Alford, DP; Compton, P; Samet, JH. *Ann Intern Med.* 2006.
* Book, SW; Myrick, H; Malcolm, R; Strain, EC. *Am J Psychiatry.* 2007.

Buprenorphine Maintenance Treatment: Chronic Pain

- Systematic review
- 10 trials involving 1,190 patients
- Due to heterogeneity of studies, pooling results and meta-analysis not possible
- All studies reported effectiveness in treating chronic pain
- Majority of studies were observational and low quality
- Current evidence insufficient to determine effectiveness of SL buprenorphine for treatment of chronic pain

Cotes, J; Montgomery, L. *Pain Medicine.* 2014.

Chronic Pain in Buprenorphine Maintained Patient

- Divide Bupe into T.I.D. or Q.I.D dosing
- ↑ Dose: e.g 4mg qid ? Ceiling effect for analgesia
- Prescribing SL Bupe Formulations for Pain is legal, but off label. For pain treatment no waiver is required, and there are no patient limits. The problem is insurance coverage and Prior Auths
- Transdermal 7 day patch (Butrans), and parenteral (Buprenex) are FDA approved for chronic pain, but are illegal to prescribe for treatment of OUD.

Module IV

Interactive Clinical Cases

Robert

- 35-year-old junior high school math teacher
- Using prescription opioids and intranasal heroin on and off since age 22
- Has been through >15 episodes of medically supervised withdrawal management
- Last treatment included a 28-day residential program during his summer break, and attending daily AA meetings
- Remained in recovery for 6 months but relapsed 3 months ago and is in some difficulty because of "calling in sick too much"

Robert

- His wife is in recovery, and insisted that he return to treatment after she discovered he was taking oxycodone pills from several doctors for a back injury following an automobile accident She is unaware that he is also using heroin daily
- Family history of alcoholism
- He denies alcohol or tobacco use
- His only current medical problem is mild asthma. His back pain has resolved
- He is hepatitis C and HIV negative

Robert

- He states…
  - "Doc, I know I'm addicted. My wife cleaned up when she was pregnant with our daughter, and she just got her 12-year chip. She moved on with her life, but I'm stuck"
  - "My back injury threw me into a tailspin. At first, I really needed the "percs", but now I'm just using them to "feel normal" and to "prevent withdrawal." I really need your help. If my wife finds out I'm back on heroin, she'll leave me this time"

Robert *questions*

- *Does Robert meet DSM-5 criteria for an opioid use disorder? If so, how?*
- *What are the treatment options for Robert?*
- *How would you assess the need for pharmacotherapy (e.g., methadone, buprenorphine, naltrexone) for Robert?*

Robert *questions*

- *Is Robert a candidate for office-based opioid treatment (OBOT) with buprenorphine/naloxone?*
- *What should the initial treatment plan include?*

John

- 48-year-old engineer requesting transfer from his methadone maintenance program to your office-based buprenorphine treatment program
- On methadone maintenance treatment program for 12 years but is tired of all the strict rules and policies
- Current methadone dose is 95 mg
- His 13 day take homes were recently discontinued when he missed his 2nd group counseling session in 3 months. He is now required to have daily observed dosing

John

- He does not think the group counseling was helping him anymore. He thinks it was helpful in the beginning but now it is just a burden
- He is caring for his sick parents along with working full time which makes it difficult for him to reliably attend his weekly afternoon counseling session
- Prior to methadone maintenance he had an 8-year history of intravenous heroin use
- Since starting methadone maintenance, he has been abstinent from heroin use

John

- He is hepatitis C positive (never treated) and HIV negative
- He has been in a stable relationship with a non-drug-using girlfriend for the past 7 years
- He wants to discontinue methadone maintenance ASAP and transfer to buprenorphine so that he can "get on with my life"

John *questions*

- *Is John a candidate for office-based opioid treatment (OBOT) with buprenorphine/naloxone? Why? Why not?*
- *What additional information do you need?*
- *If you decide John is a good candidate for transfer to OBOT with buprenorphine/naloxone what will the treatment plan include?*

Susan

- 20-year-old community college student who is requesting treatment of her heroin use
- She started using oxycodone with her roommate and is now using intranasal heroin for the last 15 months, daily for the past 3 months
- She is using about 1 gram of heroin daily
- Some of her friends are now switching to intravenous use because it takes less heroin to keep from getting sick.
- She does not want to inject drugs but may be "forced" to because she cannot keep paying the "extra cost" of sniffing heroin

Susan

- She has used all the money her parents gave her for school expenses to buy heroin, her credit cards are maxed out, and she has borrowed money from her friends
- Until last semester, she had an overall B average, but this semester she is in academic difficulty and has been told she will be on academic probation if her grades don't improve

Susan

- When she doesn't use heroin, she has anxiety, muscle aches, diarrhea and can't sleep. She recognizes the symptoms as heroin withdrawal and was surprised because she thought she could not develop withdrawal with sniffing drugs
- She smokes cigarettes ½ pack per day
- She drinks alcohol on the weekends up to 3 drinks per occasion
- She denies other drug use
- She has no prior history of addiction treatment

Susan *questions*

- *Does Susan meet the criteria for DSM 5 moderate to severe opioid use disorder?*
- *Is Susan a candidate for office-based opioid treatment with buprenorphine/naloxone? What additional information would you need to make that decision?*
- *If you decide to treat Susan with buprenorphine/naloxone, what will be your treatment plan and goals?*

Susan *continued*

- She was induced on buprenorphine in the office and given a prescription for 6 day supply of bup/nx (16/4 mg/day), and was told to participate in the clinic's 2x per week relapse prevention group and to schedule individual counseling at an off-site program
- She was told she needed to attend the relapse prevention group in order to get her next bup/nx prescription
- She returns 3 days later having taken 16/4 mg/day for 3 days
- She has not attended the relapse prevention group nor arranged for counseling

Susan *question*

- *What will be your treatment approach at this time?*

Susan *continued*

- She was partially compliant with treatment for 3 weeks including attending all but 1 of the relapse prevention groups but never started counseling
- She states she has been too busy to go to counseling. She goes to school 5 days per week and has a new job working evenings as a waitress at a pub

Susan *continued*

- *Should you require Susan to attend counseling? Why? Why not?*

Susan *continued*

- She then returns in 4 days (3 days before her follow up appointment) and states that one of her friends stole her bup/nx tablets
- Her urine is buprenorphine negative and opiate positive. She states she is sniffing heroin again to prevent withdrawal after running out of bup/nx
- She has been missing too many classes and has had to change her status to part-time student. She told her parents that she needs time away from school to figure out what her major should be
- She wants "one more chance" to restart bup/nx treatment

Susan *question*

- *What would you recommend for Susan at this point?*

Sam

- 52-years-old maintained on bup/nx 24/8 mg per day for the past 10 years
- His opioid use disorder began after a motorcycle crash resulting in multiple fractures and orthopedic surgeries. He was treated with high dose morphine and quickly escalated his use and lost control of his prescriptions
- He realized he had a problem when he ran out of his morphine and had severe withdrawal symptoms

Sam

- He believes buprenorphine is a "miracle drug" as he believes it has saved his life. He is not in counseling but attends AA 3-4 meetings per week and has a sponsor
- He has a history of alcoholism and has been sober for >20 years
- He has severe chronic right knee pain which he has been told is due to arthritis after his traumatic knee injury. His pain had been well controlled on split dose buprenorphine (8/2 mg TID), ibuprofen and acetaminophen
- Now is pain is so severe, he has had to take time off from work

Sam

- He is now being scheduled for an elective right total knee replacement
- He was told in the preoperative clinic that he needs to get off his buprenorphine for at least 5 days before his surgery
- He was told that the buprenorphine will prevent the pain medication from working and that the pain medications will likely put him into withdrawal if he is still taking the buprenorphine
- He was told to talk to you about his perioperative buprenorphine management

Sam *questions*

- *What do you recommend regarding his buprenorphine maintenance perioperatively?*
- *What do you recommend regarding his pain management perioperatively?*

Mark

- You are called by an ED colleague for advice on treating acute pain in your patient Mark who you are treating with buprenorphine maintenance…
  - 32 y.o. male with severe, 10/10, right shoulder pain after an acute dislocation and rotator cuff tear while playing flag football
  - His shoulder will be reduced and stabilized in the ED with orthopedic follow-up in 5 days

Mark

- Has a 10 year history of prescription opioid use disorder
- Has been maintained on buprenorphine 16 mg SL per day for the past 2 years
- Engaged in weekly group counseling, goes to NA meetings 2-3 times per week and has had no relapses since starting office-based treatment
- He works full-time as a mechanic at a VW dealership

Mark *questions*

- *What would you recommend for pain management in the ED?*
- *What would you recommend for pain management upon discharge from the ED?*

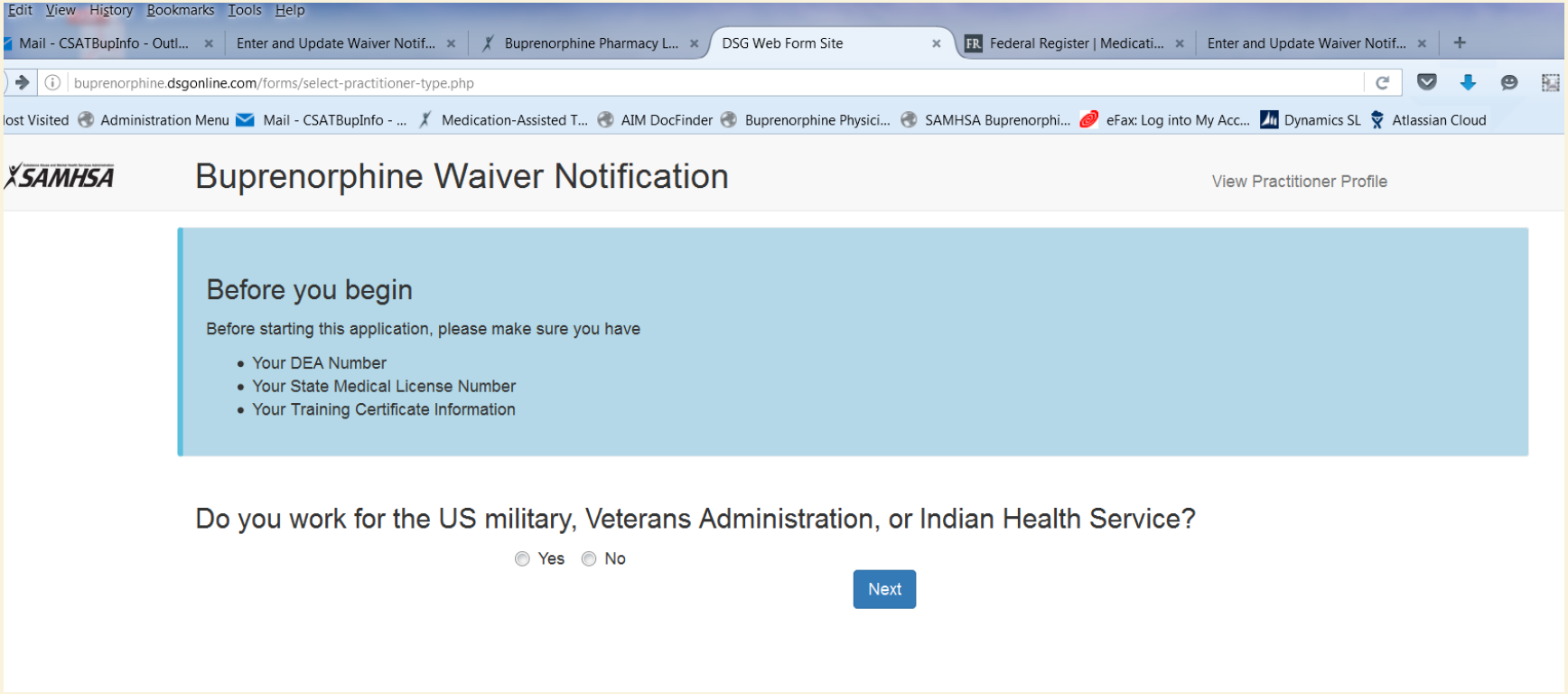
Substance Abuse and Mental Health Services Administration
SAMHSA
www.samhsa.gov • 1-877-SAMHSA-7 (1-877-726-4727)

BUPRENORPHINE Waiver Notification Form

Entering a 30 Patient Notification

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA

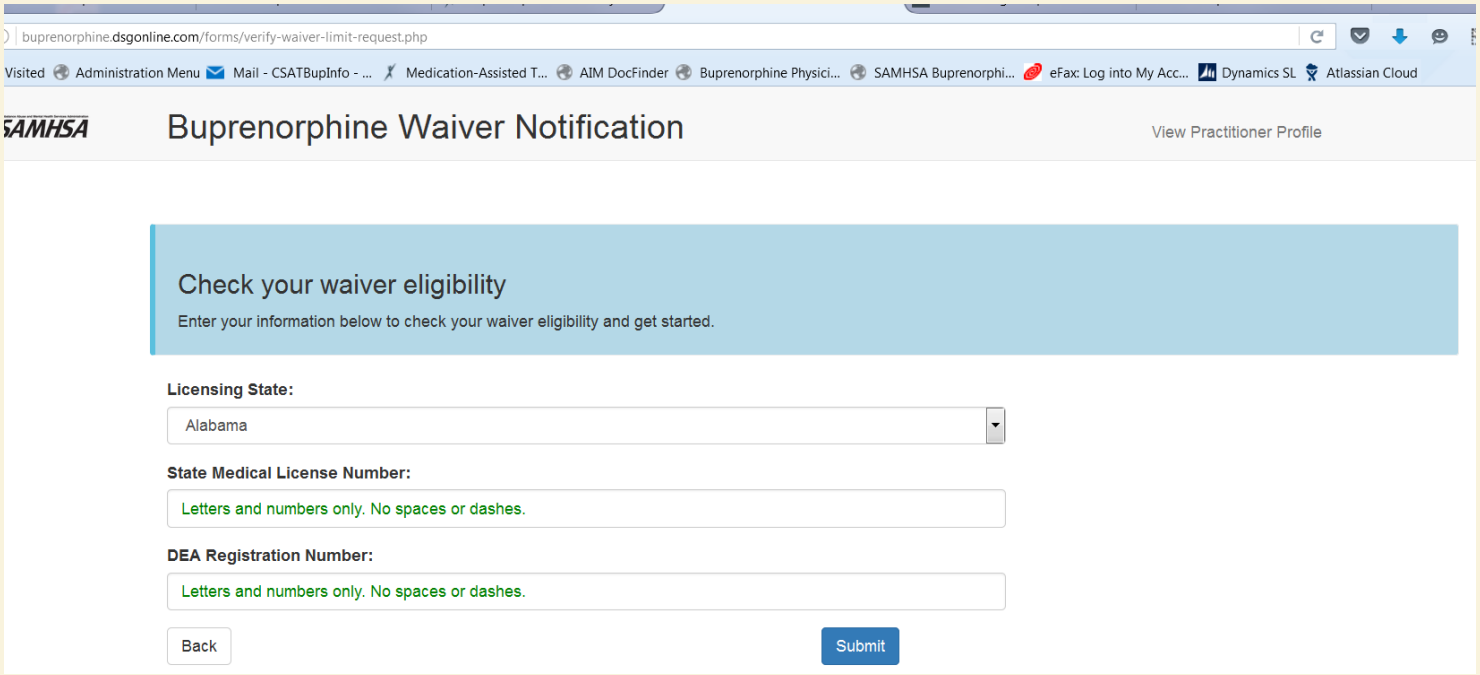
Submitting a 30 patient Notification form on line



Answer the question yes or no and click the Next button.

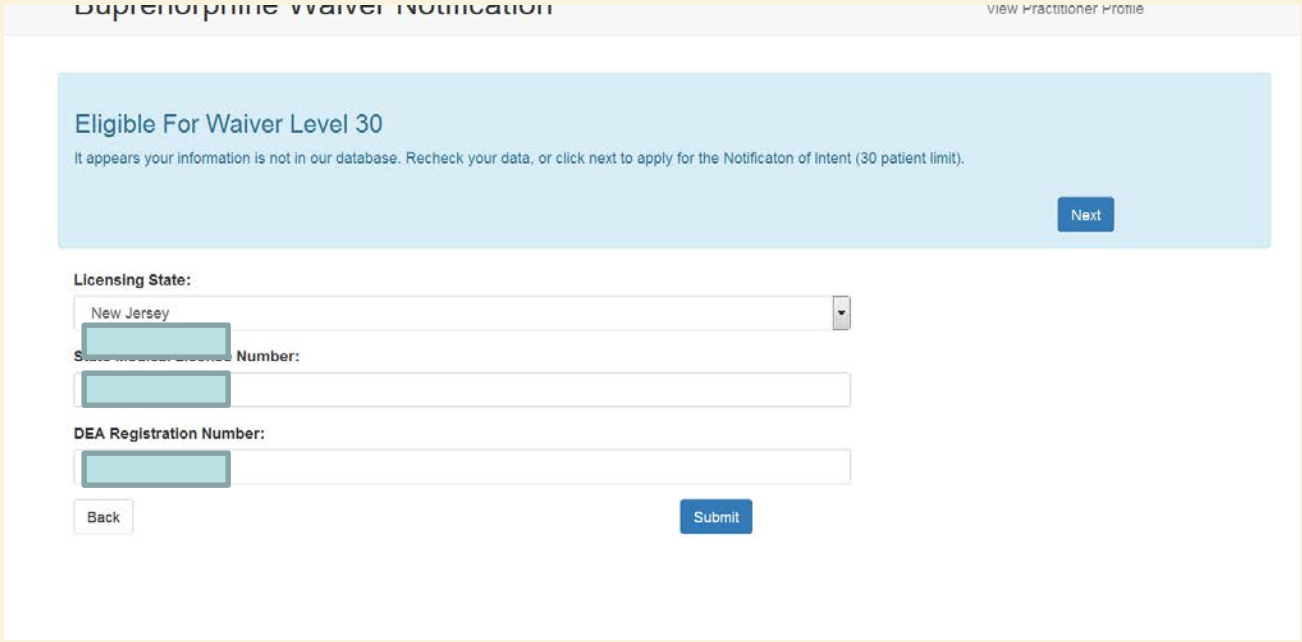
Check your eligibility

- Use the drop down menu to select your licensing state.
- Enter your medical license number, letters and numbers only. No spaces or dashes.
- Enter your DEA number, letters and numbers only.
- Click the Submit button.



Eligible?

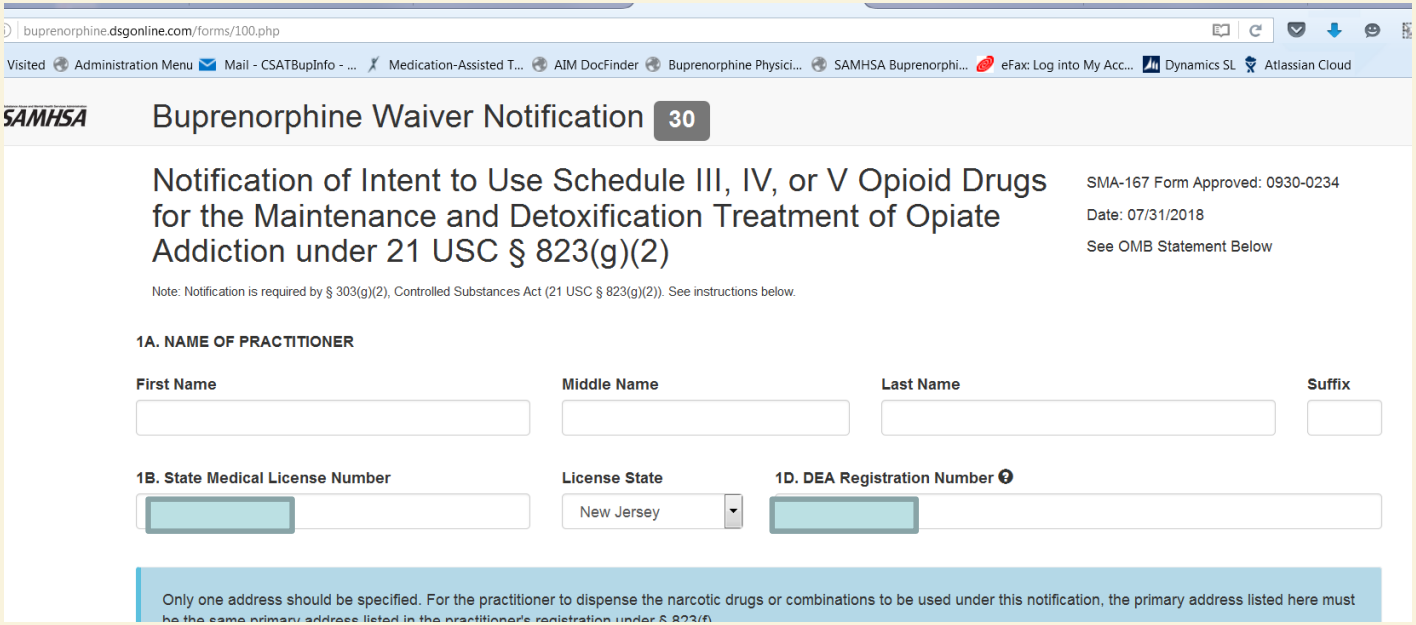
The system will indicate the number of patients you are eligible to submit a Notification for. Click the Next button.



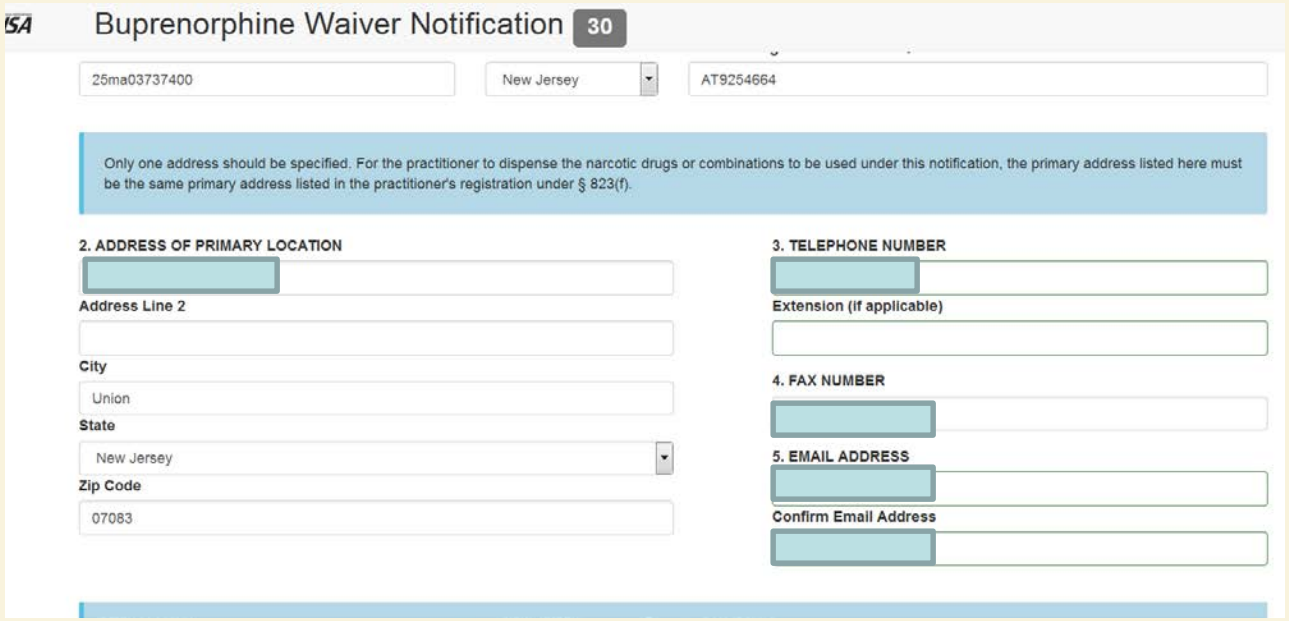
The state, medical license and DEA number will be pre-populated .

Complete Notification Form

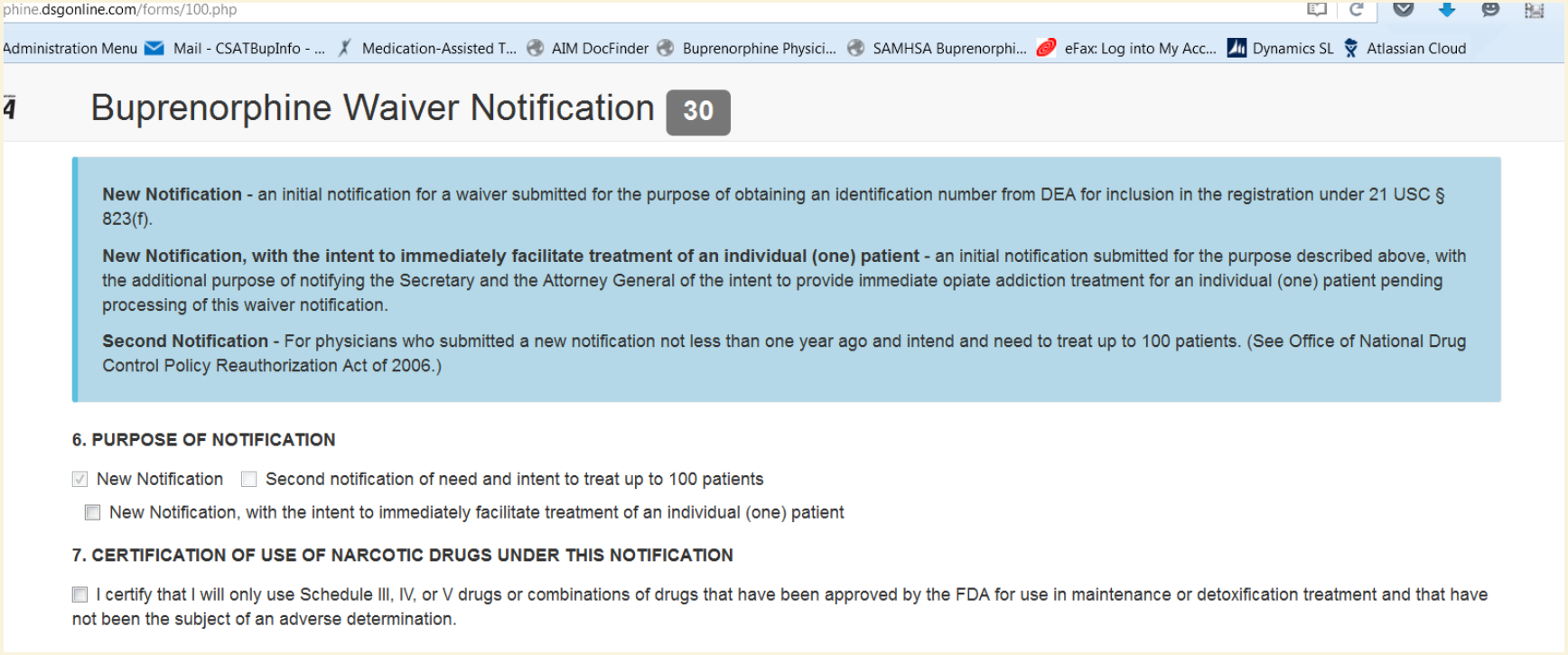
1A. Enter your name and suffix. (M.D. or D.O.)
1B. Medical license number will be pre-populated
1C. License state will be pre-populated
1D. DEA number will be pre-populated



2. Address –if you are plan to store buprenorphine on site you will need to provide the address you are listed under with DEA. Otherwise you may provide an address in your licensing state. Do not enter a P.O. Box as your street address.
3. Enter phone number
4. Enter fax number
5. Enter email address, twice. Please provide an email address the regularly access. All correspondence form SAMHSA will be via email.



6. Purpose of Notification
the New box will be pre-checked
7. Check the box, that you will only use approved Schedule III, IV, & V medications



8. Certification of Qualifying Criteria

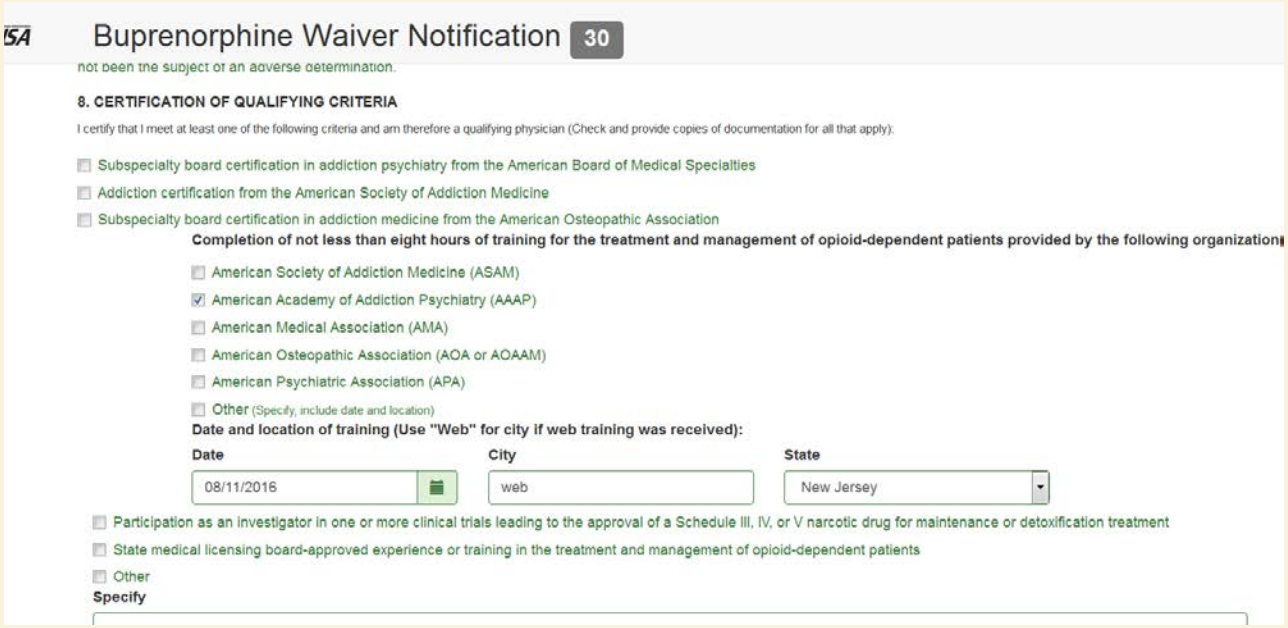
Check the appropriate box if you have a sub-specialty in Addiction medicine or psychiatry.

Check the appropriate box for the 8 hour training course you completed.

Enter the date the training was completed.

Enter the city where the training was completed. If you have complete an on-line course type "web" for your city

The state will be pre-populated but you may change it if it does not correspond with where you complete on site training.



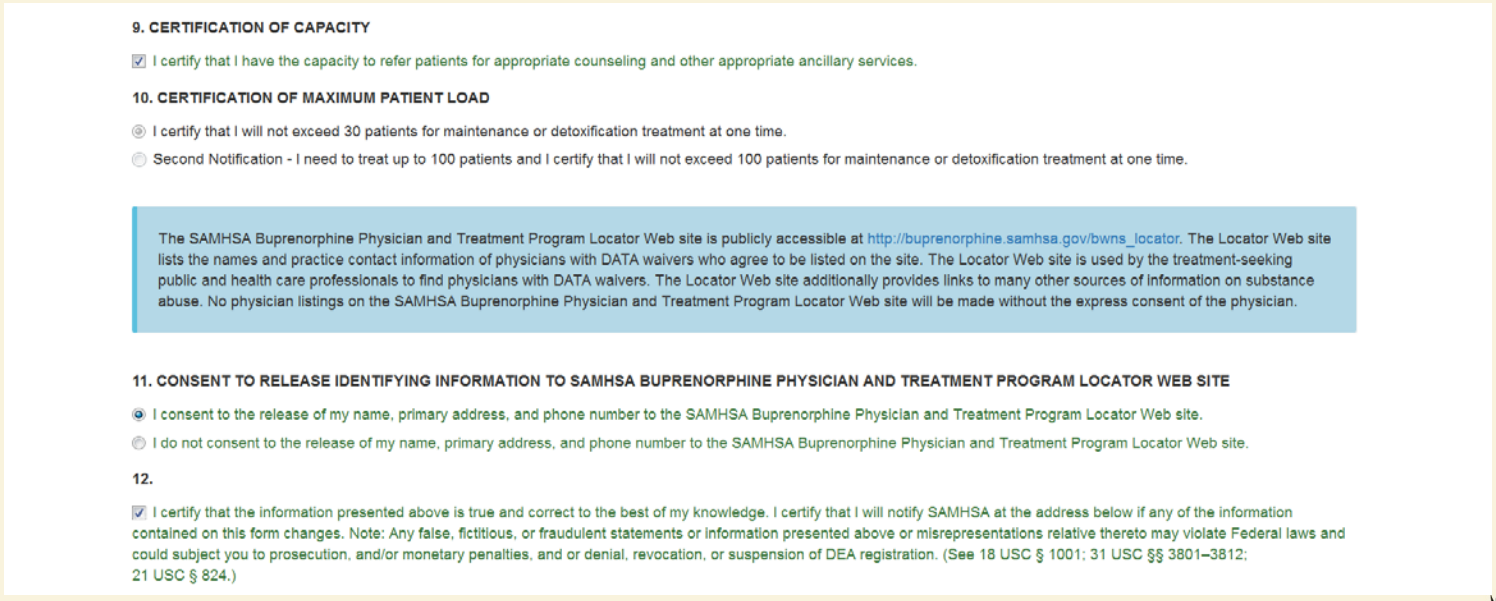
9. Certification of Capacity

Check box – must certify that you will refer patients for counseling.

10. Certification of Maximum Patient Load – button is pre-populated

11. Consent to Release Contact Information – click the "consent" or "do not consent" button

12. Check the box which states that you have not knowingly given false information.



9. CERTIFICATION OF CAPACITY

☑ I certify that I have the capacity to refer patients for appropriate counseling and other appropriate ancillary services.

10. CERTIFICATION OF MAXIMUM PATIENT LOAD

◉ I certify that I will not exceed 30 patients for maintenance or detoxification treatment at one time.

○ Second Notification - I need to treat up to 100 patients and I certify that I will not exceed 100 patients for maintenance or detoxification treatment at one time.

The SAMHSA Buprenorphine Physician and Treatment Program Locator Web site is publicly accessible at http://buprenorphine.samhsa.gov/bwns_locator. The Locator Web site lists the names and practice contact information of physicians with DATA waivers who agree to be listed on the site. The Locator Web site is used by the treatment-seeking public and health care professionals to find physicians with DATA waivers. The Locator Web site additionally provides links to many other sources of information on substance abuse. No physician listings on the SAMHSA Buprenorphine Physician and Treatment Program Locator Web site will be made without the express consent of the physician.

11. CONSENT TO RELEASE IDENTIFYING INFORMATION TO SAMHSA BUPRENORPHINE PHYSICIAN AND TREATMENT PROGRAM LOCATOR WEB SITE

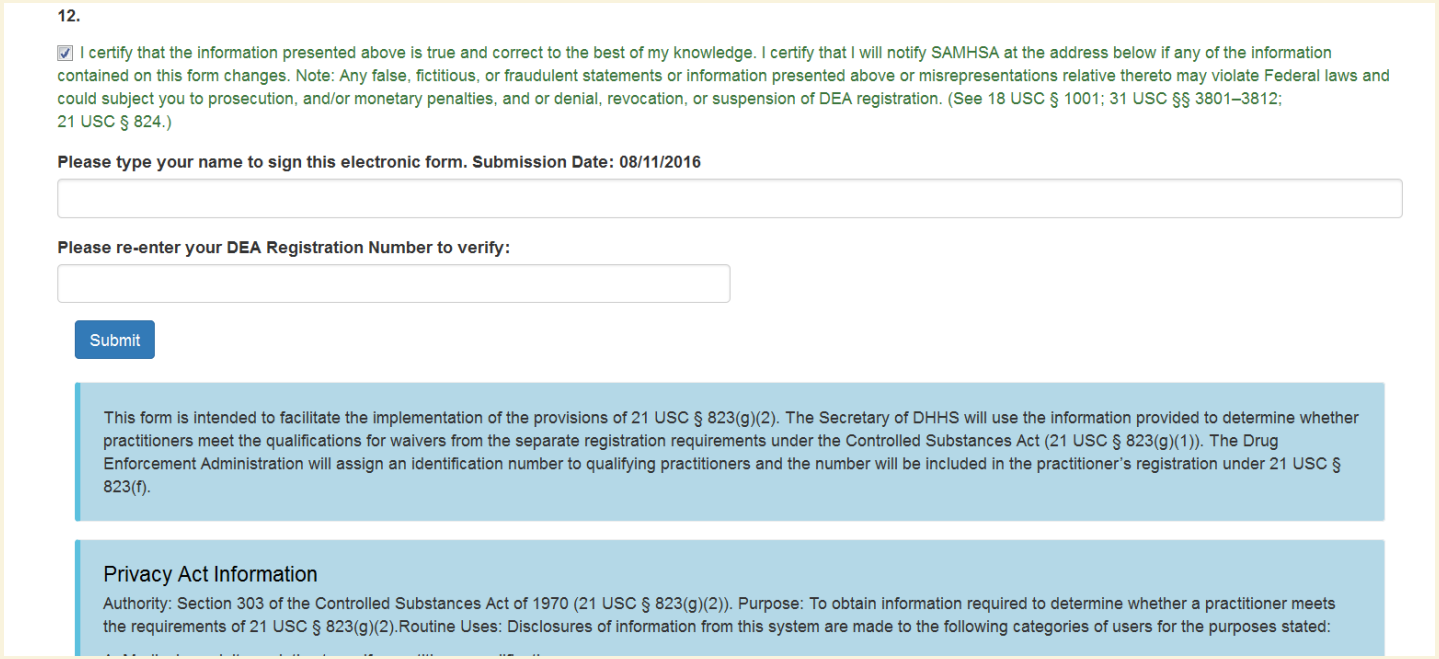
◉ I consent to the release of my name, primary address, and phone number to the SAMHSA Buprenorphine Physician and Treatment Program Locator Web site.

○ I do not consent to the release of my name, primary address, and phone number to the SAMHSA Buprenorphine Physician and Treatment Program Locator Web site.

12.

☑ I certify that the information presented above is true and correct to the best of my knowledge. I certify that I will notify SAMHSA at the address below if any of the information contained on this form changes. Note: Any false, fictitious, or fraudulent statements or information presented above or misrepresentations relative thereto may violate Federal laws and could subject you to prosecution, and/or monetary penalties, and or denial, revocation, or suspension of DEA registration. (See 18 USC § 1001; 31 USC §§ 3801–3812; 21 USC § 824.)

Type you name in the box as your signature. Type in your DEA number matching the one you entered initially. Click the Submit button.



12.

I certify that the information presented above is true and correct to the best of my knowledge. I certify that I will notify SAMHSA at the address below if any of the information contained on this form changes. Note: Any false, fictitious, or fraudulent statements or information presented above or misrepresentations relative thereto may violate Federal laws and could subject you to prosecution, and/or monetary penalties, and or denial, revocation, or suspension of DEA registration. (See 18 USC § 1001; 31 USC §§ 3801–3812; 21 USC § 824.)

Please type your name to sign this electronic form. Submission Date: 08/11/2016

Please re-enter your DEA Registration Number to verify:

Submit

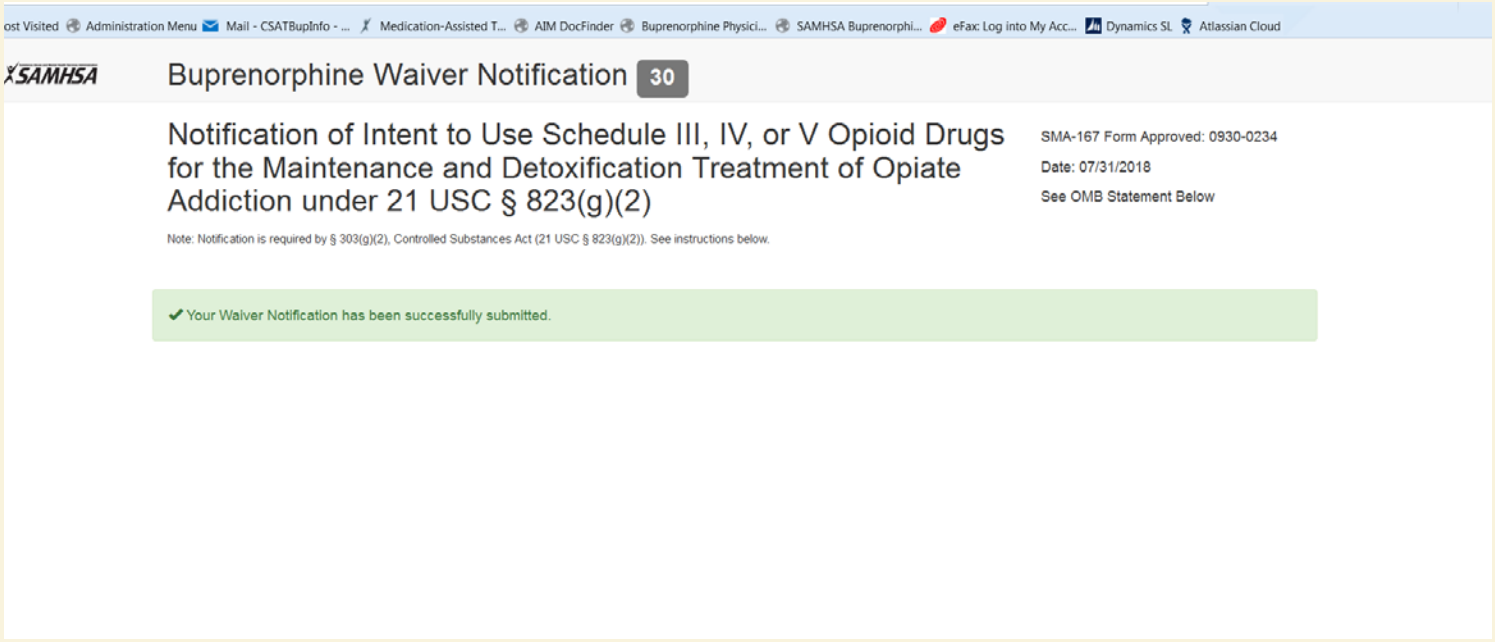
This form is intended to facilitate the implementation of the provisions of 21 USC § 823(g)(2). The Secretary of DHHS will use the information provided to determine whether practitioners meet the qualifications for waivers from the separate registration requirements under the Controlled Substances Act (21 USC § 823(g)(1)). The Drug Enforcement Administration will assign an identification number to qualifying practitioners and the number will be included in the practitioner's registration under 21 USC § 823(f).

Privacy Act Information

Authority: Section 303 of the Controlled Substances Act of 1970 (21 USC § 823(g)(2)). Purpose: To obtain information required to determine whether a practitioner meets the requirements of 21 USC § 823(g)(2).Routine Uses: Disclosures of information from this system are made to the following categories of users for the purposes stated:

When the Notification is submitted successfully you will receive a confirmation.

If it has not, an error message will indicate what needs to be corrected.



Thank You

Questions?

Email education@asam.org or call 301-656-3920