# OPIOIDS

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1

## The ASAM Board Exam Study Course in Addiction Medicine

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**Financial Disclosures**

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No Disclosures

2

## Outline

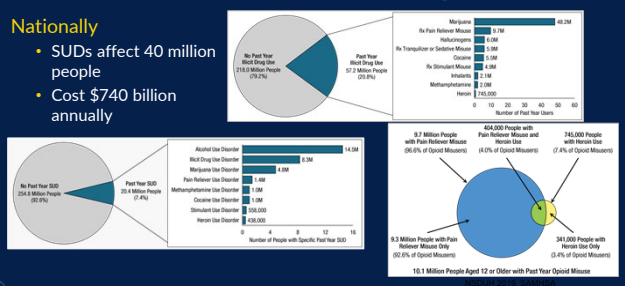
1. Opioid Use Trends
2. History
3. Regulations
4. Neurobiology
5. Intoxication and Withdrawal
6. Medication Assisted Treatment

3

## The Need for Treatment is Growing

Nationally

- SUDs affect 40 million people
- Cost $740 billion annually




NSDUH 2019, SAMHSA

4

## Unintentional Opioid Overdose

Experienced (non-fatal)

- Lifetime 24% - 94% (mean 45%, median 47%, SD 14%)
- Past Year 9% - 36% (mean 18%, median 17%. SD 10%)

Witnessed (non-fatal and fatal)

- Lifetime 48% - 96% (mean 73.3%, median 70%, SD 14%)

1 Year All Cause Mortality

- 5% of Non-Fatal Opioid Overdose Presentations to ED or Hospital Admission

Martins S et al 2015, Leece P, et al. 2020, Weiner S et al. 2020

5

## The Need for Treatment is Growing

Nationally

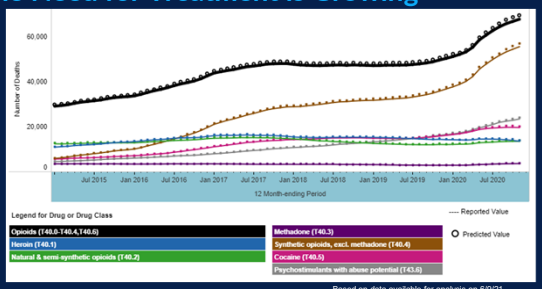
- Over 90,000 lethal ODs in 12-month period (end 11/2020), over 25% increase since prior 12-month period
- Almost 70% of all overdose deaths involve an opioid of which 2/3 include fentanyl
- Heroin users, >100% increase from 2004 to 2016
- 4 out of 5 new recent heroin users previously abused prescription opioids
- >140 OD deaths from opioids daily in US
- 2010 to 2016 heroin related deaths increased by 500%
- 2015 to 2019 fentanyl related deaths increased by over 400%

| Leading Causes of Death in US, 2019 | Annual Deaths |
|---|---|
| Heart Disease | 659,041 |
| Cancer | 599,601 |
| Chronic Lower Respiratory Diseases | 156,979 |
| Stroke | 150,005 |
| Alzheimer's Disease | 121,499 |
| Diabetes | 87,647 |
| Renal Disease | 51,565 |
| Influenza and PNA | 49,783 |
| Sepsis | 38,940 |
| Chronic Liver Disease and Cirrhosis | 38,170 |

CDC, Health Alert Network, NSDUH, SAMHSA, CSAT, NYC OCME and DOHMH Bureau of Vital Statistics

6

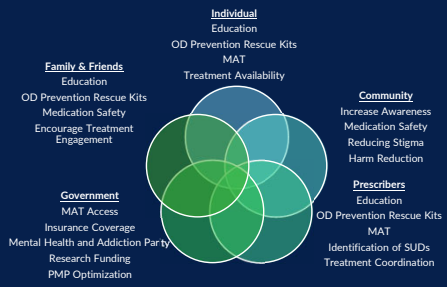
## The Need for Treatment is Growing




Based on data available for analysis on 6/9/21,
https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm#dashboard

7

## Opportunities to Reduce Risk




Hawk K et al 2015

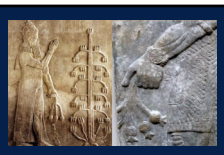
8

## Opium Poppy: Papaver Somniferum

Alkaloid Content

- **Morphine**, 7-25%, opiate analgesic, named after Morpheus, the Greek God of dreams
- **Noscapine**, 4-15%, central acting antitussive, no morphine-like effect of dependence or tolerance
- **Codeine**, 1-6%, opiate analgesic
- **Thebaine**, 1-6%, important intermediate for the synthesis of semisynthetic opioids e.g. buprenorphine
- **Papaverine**, 1-5%. smooth muscle relaxant
- Poppy Seeds: UDS→ + Opiates, Morphine, Codeine (cut-off dependent)

9



3500 BC

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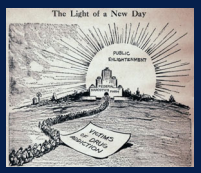


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10

## U.S. Government Involvement

Congress passes multiple laws aimed at reducing the increase in heroin/morphine/opium addiction.

- 1905-Opium banned
- 1906-Pure Food and Drug Act- labeling of all medications by pharmaceutical companies
- 1914-Harrison Narcotics Act (HNA)
  - 1919- Supreme Court sides with Treasury interpretation that physician prescribing of opioids for treatment of opioid addiction was violation of HNA
  - Later Supreme Court rulings from 1921 and 1926 reverses interpretation of HNA saying the federal government had overstepped its authority to regulate the practice of medicine

11

## U.S. Government Involvement

- 1970-Comprehensive Drug Abuse Prevention & Control Act (Controlled Substances Act)
- 1974 – Narcotic Addict Treatment Act of 1974
- 2000- Drug Addiction Treatment Act (DATA) of 2000– An Amendment to the Controlled Substances Act
  - Allows treatment of opioid dependence with narcotic schedule III, IV, V, or combinations of such drugs
  - Buprenorphine designated Schedule III and FDA approved for treatment of opioid dependence
  - Capacity to refer patients for counseling

12

## U.S. Government Involvement

- Approved training programs
  - Complete eight hours of training provided by a pre-approved society or by a society approved by State Medical Licensing Boards or by the Secretary of HHS
  - Providers Clinical Support System, ***PCSSNOW.ORG***
- Apply for waiver from Center for Substance Abuse Treatment (CSAT)
- 2006 – Patient limit increases to 100
- 2016 Comprehensive Addiction and Recovery Act (CARA)
  - Expands buprenorphine prescribing to PA and NP, qualify after taking 24hr of training, until 2021.
  - SAMHSA authorizes patient limit increase to 275

13

13

## U.S. Government Involvement

- 2018 Support for Patients and Communities Act
  - Expands buprenorphine prescribing to Clinical Nurse Specialists, Certified Registered Nurse Anesthetists, and Certified Nurse Midwives until 10/1/23
  - Increases number of patients to 100 that can be treated by certain physicians in the first year of obtaining a waiver under specific conditions.
- 2020 HHS Public Health Emergency Declaration, DEA partners with SAMHSA (temporary)
  - Controlled Substances (in accordance with DATA 2000 waivers) can be prescribed using telemedicine or telephone without first conducting an in-person examination while HHS PHED in effect
  - OTP utilization of methadone continues to require an initial on-site examination but attendance restrictions related to time in treatment have been temporarily modified.

14

14

## U.S. Government Involvement

- 2021 HHS Updates Practice Guidelines for the Administration of Buprenorphine for Treating OUD
  - Provides an alternative Buprenorphine Waiver Notice of Intent allowing providers to treat up to 30 patients to forego training requirement, as well as certification to counseling and other ancillary services.
    - https://buprenorphine.samhsa.gov/forms/select-practitioner-type.php
    - Physicians select "Other" in "CERTIFICATION OF QUALIFYING CRITERIA," then enter "practice guidelines" in the text box for the city of the training. The training date should be the application date.
    - Mid-level practitioners (APRNs and PAs) select SAMHSA's Providers Clinical Support System (PCSS) in "CERTIFICATION OF QUALIFYING CRITERIA," then enter "practice guidelines" in the text box for the date.

As of June 2021 over 100,000 practitioners hold waivers, 71,000 with 30-limit, 22,000 with 100-limit, <10,000 with 275-limit

15

15

## Terminology

Endorphins- describes the whole class of endogenous opioid ligands
- Beta-endorphin, enkephalin, dynorphin

Opioid- describes entire class of non-endogenous (natural or synthetic) and endogenous compounds that bind to one or more types of opioid receptors
- Methadone, fentanyl, oxycodone

Opiate- describes compounds naturally derived from the poppy plant
- Morphine, codeine

16

16

## Endogenous Opioids & Opioid Receptors

| Opioid Class | Opioid Receptor Type |
|---|---|
| Beta-endorphin<br>Endomorphin | Mu Opioid Peptide Receptor |
| Dynorphin | Kappa Opioid Peptide Receptor |
| Enkephalin | Delta Opioid Peptide Receptor |
| *Orphanin/Nociceptin (opiate-like)* | *Nociceptin/Orphanin FQ Peptide Receptor, Opioid Receptor Like-1* |

Multiple opioid receptor polymorphisms identified[7]

17

17

## Overview

Addictive drugs produce an enhancement in extracellular dopamine levels in the nucleus accumbens and other limbic structures as well as cortical areas.

Endorphin-Opioid Receptor binding results in an increase in dopamine release in the mesolimbic and mesocortical pathways but unlike exogenous Opioid-OR binding the effect is less robust and does not result in habituation.

18

18

## Opioid Receptors

All Opioid Receptors
Seven transmembrane domain
G protein-coupled
Primarily inhibitory pathways

**Mu Opioid Receptor (OPRM) Activation (predominantly beta-endorphin)**
Reduces cAMP
Inhibits transporter release of GABA, glycine, and glutamate
- Inhibition of GABA in ventral tegmental area (VTA)→increases dopamine release throughout mesolimbic (amygdala, ventral pallidum, hippocampus, NAcc)-mesocortical (prefontal cortex, orbitofrontal cortex, anterior cingulate) dopaminergic fields.

19

19

## Opioid Receptors

**Mu Opioid Receptor (OPRM) Activation (predominantly beta-endorphin)**
Widely dispersed across a wide variety of brain regions, including cortex, striatum, thalamus, hippocampus, locus coeruleus, ventral tegmental area, nucleus accumbens, amygdala

Mu receptors also mediate rewarding properties of non-opioid drugs of abuse including cannabinoids, alcohol and nicotine, or even natural reinforcers such as social interactions

Physiologic effects of **intoxication** and **withdrawal**

20

20

## Opioid Receptors

**Kappa Opioid Receptor (OPRK) Activation (predominately dynorphin A)**
Identified in various CNS regions such as the nucleus accumbens, caudate–putamen, olfactory tubercle, bed nucleus of the stria terminalis, medial preoptic area, paraventricular nucleus, supraoptic nucleus, dorsomedial, and ventromedial hypothalamus, amygdala, midline thalamic nuclei, periaqueductal gray, raphe nuclei, parabrachial nucleus, locus coeruleus, spinal trigeminal nucleus, and the nucleus of the solitary tract.

Mediates **dysphoric** activities of both opioids and cannabinoids and therefore opposes mu receptors in regulating the hedonic tone and modulating stress-induced relapse.

21

21

## Opioid Receptors

**Delta Opioid Receptor (OPRD) Activation (predominately enkephalin)**
Identified in various CNS regions including thalamus, amygdala, NAcc, locus coeruleus, VTA, and others

Lack of familiar opioid characteristics like respiratory depression, reinforcing effects as measured in self-administration studies, and opioid (mu or kappa) withdrawal symptoms.

Delta receptors are less directly involved in hedonic control.

Distinct from mu and kappa receptors, delta receptors may play a role in emotional responses and show **anxiolytic** activity along with benefits in analgesia resulting from inflammatory states.

22

22

## Genetics/Pharmacogenomics

Multiple polymorphisms identified in opioid receptor genes and other coding regions which have clinical effect

OPRM1 chromosome 6; OPRK1 chromosome 8; OPRD1 chromosome 1

OPRM1 Gene→SNP,rs1799971: **A118G** (Adenine to Guanine substitution) → Asn40Asp(Substitution in the receptor extracellular domain) → ↑(?) Binding beta endorphin, ↑ risk OUD, AUD, ↓(?) Analgesic Response

CYP 2D6: Codeine→Morphine, Hydrocodone→Hydomorphone, Oxycodone→Oxymorphone (Asian heritage: ↓↓ 2D6 Other Groups ~ 10% PM)

Methadone: CYP 3A4, 2D6, 2B6

COMT (enzyme) The most widely studied variant is **158Met**, where a G to A nucleotide substitution at codon 158 results in an amino acid change from valine to methionine. Patients with Met/Met genotype have lower morphine requirements than those with a Val/Val expression.

23

23

## Role of Endorphin Systems in Normal Physiologic Functions

- Endogenous response to pain
- Neuroendocrine functions
  - Stress-response systems including HPA axis
  - Reproductive function including HPG axis
- Immunologic function
- Gastrointestinal function
- Cardiovascular function
- Pulmonary function
- Mood, affect, cognition

24

24

## Additional Opioid Effects

- CNS → Sedation, Analgesia, Euphoria
- GI → Constipation, Nausea
- Endo → ↓Testosterone, ↑Prolactin , ↓FSH, LH
- Urinary → Retention
- Cardiovascular → Vasodilatation, ↑QTc
- Miosis
- Tolerance Varies

25

25

## Opioids of Note

- Fentanyl ↑ Temp → ↑Skin Absorption
- Meperidine → Normeperidine→ Neuroexcitation, MAO interactions Serotonin Syndrome
- Tramadol weak mu, ↑5HT, ↑NE, Seizures, (Sched. IV), serotonin syndrome
- Tapentadol mu agonist, ↑ NE (5HT), serotonin syndrome
- Kratom, low dose (1-5g) stimulant resembling caffeine/cocaine, high dose (5-15g) opioid like effects, analgesic/sedation reversed by naloxone, possible assoc with hepatic cholestasis—dose dependent
- Tianeptine, antidepressant similar to TCAs, mu and delta agonist, anticholinergic

26

26

## Opioid Potency

| Opioid | Relative Potency | Lethal Dose |
|---|---|---|
| Morphine | 1x | 1 Pea |
| Diacetylmorphine (heroin) | 2x | 1 Sun Flower Seed |
| Fentanyl | 100x | 1 Sesame Seed |
| Sufentanil | 500x | 1 Grain of Sand |
| Carfentanil | 10,000x | 0.5 Grain of Salt |

27

27

## Role of Medications in the Treatment of Opioid Use Disorder

Overdose
- Acute intervention, possible reversal, and close monitoring

Withdrawal/Early Stabilization
- Reduction and stabilization of withdrawal symptoms
- Opportunity to initiate and engage in ongoing addiction treatment

Maintenance Therapy
- Prevents or eliminates withdrawal
- Diminishes or eliminates drug craving and use of illicit opioids
- Blocks or attenuates the effects of heroin and other abused opiates
- Risk/harm reduction, reduces overdose risk
- Increased treatment retention and engagement in comprehensive rehabilitation
- Decreased medical and psychiatric symptoms, improves health, reduced risk of HIV and Hep C infection
- Improved social determinants such as employment, family relations
- Decreased criminal behavior

28

28

## Opioid Overdose

***Classic Triad Seen In Overdose***

- ***Miosis (Dilated With Prolonged ↓PO2)***
- ***Decreased level of Consciousness/Coma***
- ***Respiratory Depression***
- Pulmonary Edema (Non-cardiogenic)
- Seizures
  - Meperidine, Tramadol

29

29

## Management of Opioid Overdose

- Ventilatory support if needed
- Parenteral Naloxone
- If IV access, bolus 0.1mg/min titrated to
  - RR>10/min
  - Improved level of consciousness
  - No withdrawal
  - If needed ongoing IV infusion 2/3 of initial bolus dose/hr.
- If no IV access, 0.4-0.8mg SQ or IM and observe
- Naloxone OD Prevention Kits

30

30

## Opioid Overdose Education and Naloxone Distribution (OEND) Programs

- From 1996 to 2014, >150,000 trained with >25,000 reported overdose reversals. MMWR June 19 2015
- Improved trainee Strang 2006 knowledge of OD safely and effectively administer naloxone
- Some evidence suggests trainees reduced IV use and were more likely to enter treatment 6 months after training. Seal 2005
- Chicago, OD deaths reduced after introduction of OOPPs. Maxwell S 2006
- Mass, ↓27% in OD deaths low implementation (1-100/100k) vs ↑46% in high implementation (>100/100k). Walley AY 2013
- But still…
- Study of >500 MDs reported 54% would NEVER consider prescribing naloxone to an IVDU. Beletsky L 2007

31

31

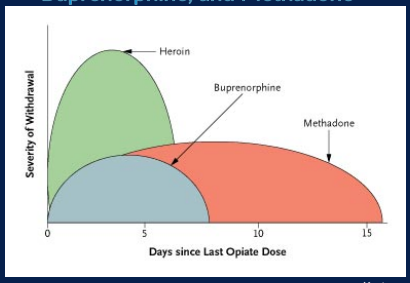
## Pitfalls Opioid Analgesic ODs

- Need for repeated naloxone treatment with longer acting opioids (methadone), and more potent opioids (fentanyl, carfentanil)
- Check for Fentanyl Patch under clothing
- Fentanyl chest wall/skeletal muscle rigidity
  - Most common with rapid IV administration, not dose related
  - Ventilation, naloxone, neuromuscular blocking agent
- Observation
- Alert to possible acetaminophen or other OD

32

32

## Severity of Opioid-Withdrawal Symptoms after Abrupt Discontinuation of Equivalent Doses of Heroin, Buprenorphine, and Methadone




Kosten and O'Connor, 2003

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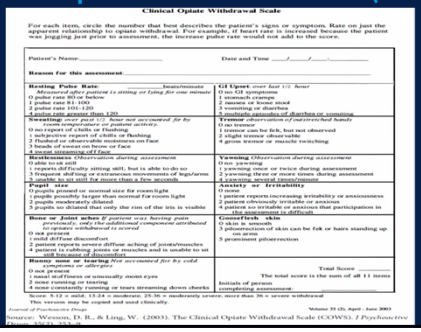
## Clinical Opiate Withdrawal Scale (COWS)

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## Clinical Opiate Withdrawal Scale (COWS)

- Methadone—Hospitalized, OTP, very limited other licensed OP
- Buprenorphine---Hospitalized, Recent HHS Practice Guideline change to Notice of Intent, Waivered MD/DO/PA/NP, OTP
- Symptomatic Meds, e.g. Clonidine, NSAIDS, Imodium, B/Zs
- 72 Hour Rule: Dispense Only

**Table 2. Medication Treatment for Opioid Withdrawal.***

| Protocol | Examples | Effects and Comments |
|---|---|---|
| Medication | | |
| Opioid agonists | Methadone (20 to 35 mg daily) or buprenorphine (4 to 16 mg daily), tapered over several days or weeks | Withdrawal symptoms are decreased in severity. Methadone and other opioid agonists are currently restricted to inpatient settings or licensed programs; buprenorphine is now approved by the FDA for this purpose. |
| Nonopioid drugs | Clonidine (0.2 mg 3 times daily) or lofexidine (0.2 mg twice daily), administered for approximately 10 days for heroin and 14 days for methadone | Withdrawal symptoms are decreased in severity. Lofexidine is less likely to produce hypotension but is not currently approved by the FDA for this purpose. |
| Rapid and ultra-rapid detoxification | Protocols include a variety of medications: opioid antagonists (naloxone or naltrexone), clonidine, sedatives, antiemetic agents, analgesics, anesthetics | Withdrawal is precipitated with an opioid antagonist, and symptoms are managed with a variety of adjuvant medications. Patients are awake or lightly sedated for rapid detoxification; they are under heavy sedation or general anesthesia for ultra-rapid detoxification. Both methods require special training, equipment, or both. Research on efficacy is limited. |

* FDA denotes Food and Drug Administration.

35

35

## Opioid Use Disorder Treatment Outcome*

| | |
|---|---|
| **Methadone Maintenance** | **50 – 80%** |
| **Buprenorphine-Naloxone Maintenance** | **40 – 70%**** |
| **Naltrexone Maintenance (oral, depot)** | **10 – 20%, 20-60%***** |
| **"Drug Free" (non-pharmacotherapeutic)** | **5 – 20%** |
| **Short-term Detoxification (any mode)** | **5 – 20% (limited data)** |

** One year retention in treatment and/or follow-up with significant reduction or elimination of illicit use of opiates*
*** Maximum effective dose (24mgsl) equal to 60 to 80 mg/d or possibly even greater of methadone.*
**** 6 month treatment with extended release naltrexone*

***Methadone and Buprenorphine maintenance treatment reduces overdose risk by 44-86%***

Kreek 1996, 2001, 2003, 2006, Krupitsky 2011, Fudala 2003, Weiss 2011, Woody 2008, Mattick 2009, Lee 2016+2017

36

36

## Buprenorphine

Onset of action 30-60min

Peak effect 90-100min, half-life 24-42 hr

Metabolism via CYP 3A4 isoenzyme

- Those on CYP 3A4 inhibitors (azole, antifungals, macrolide antibiotics, and HIV protease inhibitors) should be closely monitored, and dose adjustments may need to be made
- Those on CYP 3A4 inducers (phenobarbital, carbamazepine, phenytoin, and rifampin) should also be monitored, and dose adjustments may need to be made

Can alter liver enzymes

- Liver function should be monitored periodically depending upon any recent symptoms or history of hepatitis
- Consider dose reduction or transition to mono formulation if ≥3x upper limit of normal

Pregnancy

- **MOTHER study**, mono (without naloxone) formulation, reduced morphine/hospitalization/NAS

37

37

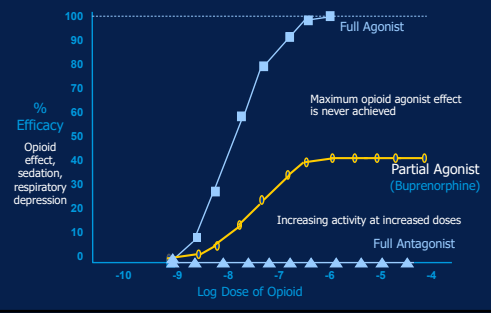
## Buprenorphine

- Buprenorphine is a partial agonist of the μ-opioid receptor and antagonist of the κ-opioid receptor.
  - *High affinity* for μ-opioid receptor
    - Competes with other opioids and inhibits their effects
  - *Slow dissociation* from μ-opiate receptor
    - Prolonged therapeutic effect
- At low doses, acts as an agonist; at high doses or in patients dependent on high doses of chronic opioids, it has the ability to act as an antagonist.

38

38

## Partial Agonist: Ceiling Effect

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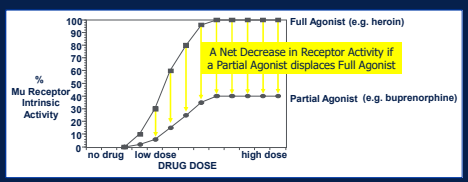
## Buprenorphine Precipitated Withdrawal

- Displaces a full agonist off the mu receptors
- Buprenorphine only partially activates receptors
- Net decrease in activation occurs and withdrawal develops

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## Abuse and Overdose Potential

Buprenorphine has limited abuse potential (epidemiological, human laboratory studies show)

- Relatively low compared to other opioids

Diversion and illicit use of analgesic form (by injection)

Overdose risk low

- Partial μ-OR agonist results in limited CNS and respiratory depression in those with physical dependence
- Risk higher with combined abuse of other sedatives e.g. benzodiazepine
- Deaths more associated with mono formulations dissolved and injected with concurrent benzodiazepine use

41

41

## Induction

Moderate Opiate Withdrawal Symptoms

- 6-18 hrs after last use of short-acting opioids (heroin, oxycodone), or 24-48 hrs after longer-acting opioids (methadone)
- Clinical Opiate Withdrawal Scale (COWS) score of ≥8-10
- Toxicology testing:

| | Minutes | Hours | Days | Weeks | Months |
|---|---|---|---|---|---|
| Blood | | | | | |
| Breath | | | | | |
| Oral Fluid | | | | | |
| Urine | | | | | |
| Sweat | | | | | |
| Hair | | | | | |

42

42

## Induction

Day 1: Start with buprenorphine (+/-naloxone) 2-4 mg SL
- Consider additional 2-4mg after 1-2 hrs if continued elevation of COWS and no precipitated withdrawal
- May consider additional 2-4 mg 6-8 hrs later if significant OWS persist
- Total Day 1 dose 8 mg

Day 2: Provide total day 1 dose (routinely given as single dose)
- May increase by 4mg twice daily for ongoing symptoms (8 mg total)
- Total Day 2 dose 16 mg

Adjuvant medications:
- Clonazepam 0.5 to 1mg tid prn, Clonidine 0.1 to 0.2mg q4 prn, Trazadone 100mg qhs prn, NSAIDS, Antiemetics/GI (promethazine 25mg IM, loperamide 4mg PO, octreotide 50 mcg SQ), IVF

43

43

## Induction Continued

- Typically initiated for outpatients at-home with physician instructions and availability, and during hospitalizations or ED assessments.
- May be carried out using either Bup/Nal or Bup mono, dependent upon the physician's judgment.
  - Bup/Nal commonly utilized but may consider bup mono formulation for those pregnant, severe liver disease, allergic rxn.

44

44

## ED Initiated Buprenorphine Treatment

- Similar to other routine ED-based interventions for medical conditions
  - Buprenorphine induction acutely stabilizes and serves to initiate treatment of OUD
  - Facilitate linkage to community-based providers of OBAT
- From 2009 and 2013, 329 randomized to Screening+Referral, SBIRT, or SBIRT+bup induction in ED and appt for OBAT within 72hrs.
  - At 30 days
    - Increased engagement in addiction treatment: 37%, 45%, 78% (p<.001)
    - Decreased illicit opioid use in past 7 days: 2.3 days, 2.4 days, 0.9 days (p<.001)
  - At 2 months
    - Increased engagement in addiction treatment: 43%, 47%, 74% (p<.001)
    - Decreased illicit opioid use in past 7 days: 1.8 days, 2.0 days, 1.1 days (p=.04)

D'Onofrio 2015, 2017

45

45

## Buprenorphine

- Long-acting subdermal implant, FDA approved 2016
  - Low, steady state dose for 6 months
  - Intended for use only after clinical stability on a daily dose of 8mg or less.
  - 4 approx. 1 inch long implants requiring a minor surgical procedure for both insertion and removal.
  - Requires completion of in-person training.
  - Non-inferior percentage of urine samples negative for opioids, with favorable findings complete abstinence and time to first use of illicit opioids at 24 weeks compared to SL buprenorphine of 8mg or less.

Rosenthal 2016

46

46

## Buprenorphine

- Extended-release monthly injection, FDA approved 2017, available 2018
  - Monthly subcutaneous (initial 300mg x 2, followed by maintenance 100mg).
  - Pt initially inducted onto once daily buprenorphine of 8-24mg for 7-10 days.
  - Compared to placebo, increased opi neg tox or self-reported opi use and higher proportion without any evidence of illicit opioid use. (FDA report 2017)

Transdermal and parenteral analgesic formulations not approved for OUD, only pain

47

47

## Naltrexone

- Long-acting, competitive, non-selective opioid-antagonist with highest affinity to mu-opioid receptors.
- Metabolism via CYP450
- Excretion predominately urine (53-79%), partial feces. 2% excreted unchanged
- Active metabolite 6-beta-naltrexol
- Half-life 4hours for naltrexone and 13 hours for 6-beta-naltrexol
- High doses may be associated with hepatic toxicity, contraindicated if elev transaminases, no known hepatic toxicity at standard doses

48

48

## Naltrexone

- Oral formulation FDA approved 1984
  - Once daily, 3xweek alternative
  - Low adherence limits use to highly motivated populations (Cornish 1997, Roth 1997)
- Completion of withdrawal treatment must precede naltrexone treatment for those with current physical dependence
- POC toxicology
- Consider induction protocol prior to naltrexone initiation (Sigmon 2012)

49

49

## Naltrexone

Long-acting injectable formulation (naltrexone-XR), FDA approved for OUD in 2010

- More effective than placebo Comer 2006, Krupitsky 2011, Tiihonen 2012
- More effective than treatment as usual in criminal justice population Lee 2016
- Lower medical/surgical related hospitalizations but not overall healthcare utilization found in those in criminal justice system as compared to TAU. Lee 2018
- Non-inferior to buprenorphine, when randomization occurred after opioid detoxification or those successfully inducted onto XR-NTX. Tanum 2017, Lee 2018
- While the number of reported OD in studies to date is low, most studies did not report clearly how overdose events were measured, particularly in those lost to follow-up.
  - Given high dropout rates and known OD risk of interrupted/stopping treatment, rigorous evaluation and reporting of fatal/nonfatal ODs remains needed. Jarvis 2018

50

50

## Naltrexone - XR

*Initial Readiness Assessment*

- Vital signs, urine toxicology (screen for all opioids including, buprenorphine, oxycodone and methadone), recent opioid use history, pregnancy test, assess for contraindications, e.g. active pain requiring opioids

*Last Opioid Use ≥14 days*

- IF: Good evidence of opioid abstinence in past 2 weeks, no withdrawal symptoms, and opioid-negative toxicology.
- THEN: Proceed with the XR-naltrexone injection.

XR-Naltrexone: A Step-by-Step Guide, PCSS 2017

51

## Naltrexone - XR

*Last Opioid Use 8-13 days ago, evaluate for withdrawal using COWS*

- If COWS >4 treat withdrawal with adjunctive medication and reevaluate in 1-2 days.
- If COWS ≤4 AND opioid-negative toxicology, perform naloxone challenge. If negative, proceed with the XR-naltrexone injection. If positive, adjunctive medication and reevaluate in 1-2 days.

*Last Opioid Use ≤7 days*

- Patient may still be physically dependent even with opioid-negative toxicology.
- Treat withdrawal with adjunctive medication and postpone evaluation until at least 7 days of no opioid use (See USE within 8-13 days).
- In case of daily opioid use, recommend cessation and conduct buprenorphine-assisted withdrawal management.

XR-Naltrexone: A Step-by-Step Guide, PCSS 2017

52

## Naltrexone/ Naltrexone Challenge Test

**Naloxone (IM) Challenge Procedure**

- Obtain baseline COWS, if 4 or less proceed with the challenge
- Administer naloxone 0.4 mg (1 cc) IM to deltoid and observe for 20 minutes.
- If no change in COWS administer additional 0.8 mg (2 cc) to the other deltoid and monitor for additional 20 minutes
- Test is considered positive if there is a COWS increase of 2 or more from the pre-injection score

**Naltrexone (PO) Challenge Procedure**

- Obtain baseline COWS; if 4 or less proceed with the challenge
- Administer naltrexone 25 mg p.o. and observe for 90 minutes
- Test is considered positive if there is a COWS increase of 2 or more

XR-Naltrexone: A Step-by-Step Guide, PCSS 2017

53

## Naltrexone - XR

**Buprenorphine-assisted Withdrawal Management for Naltrexone-XR Initiation**

- Wait until the patient is in withdrawal (COWS > 8) and administer buprenorphine (4 mg bid on Day 1)
- Administer adjunctive medications as needed to alleviate residual withdrawal
- Continue adjunctive medication for at least 7 days after the last day of buprenorphine
- Perform naloxone/naltrexone challenge before administering XR-naltrexone

XR-Naltrexone: A Step-by-Step Guide, PCSS 2017

54

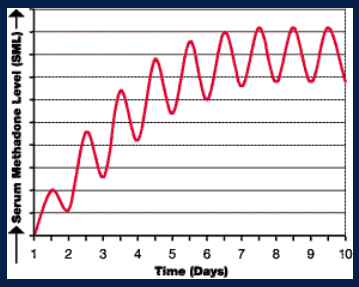
## Methadone

- Approved by FDA 1972 for opioid dependence
- Mu opioid receptor agonist and NMDA antagonist (reduces development of tolerance)
- 2 enantiomers in equal amounts
  - *l (R)* active, *d (S)* inactive
  - Rapidly absorbed orally with detectable plasma levels at 30min but has a delayed onset of action with peak levels at 2-4 hours with sustained levels for 24 hours.
- Metabolized by CYP450 – several isoforms:
- CYP2D6 – may explain group who need very high doses
- Excreted in urine and feces
  - Avoids accumulation and reduces risk of toxicity for those with renal or liver dysfunction
- Half-life 24-36 hrs but may range from 4-91 hrs

55

55

## Steady State




56

56

## Methadone

- 2006 Black Box Warning – risk of QTc prolongation and possibly torsades de pointes/polymorphic VT, dose dependent
- Common side effects: ***constipation, diaphoresis, to a lesser extent sexual dysfunction***
- Safety profile well established including during pregnancy
- ***Beware Opioid Conversion Tables!***
- ***Serum Level*** – clinical presentation should direct dosing decisions but SML can serve as aid
  - Peak level drawn 2-4 hours after dosing
  - Trough level drawn prior to daily dosing ~24hrs
  - Peak SML less than twice trough

57

57

## Methadone

1. **Initial dose** 10-20mg PO (50% dose IM), 20mg eliminates severe withdrawal (not routinely recommended to exceed 30mg in first 24 hours)
2. **Craving** reduced by increasing methadone dose by 5-10mg q three to seven days (80-120mg or greater)
3. **"Blocking dose"** (often 80-120mg or greater): tolerance that inhibits the euphoric high

**After stabilization, methadone and buprenorphine do not produce euphoria or sedation**

ASAM 2017, 2015, SAMHSA TIP 63

58

58

## The Basics for all OTPs

- Comprehensive Assessments
- Treatment Plans
- Toxicology Testing
- Diversion Control
- Broadening of MAT options from methadone to incorporation of buprenorphine, etc.
- Attendance schedule for medication dispensing
- Guest Medication
- Confidentiality, 42 CFR Part 2
- Regulatory Oversight

59

59

## Medication and Treatment Setting – Selection Considerations

- Abstinence to Harm Reduction Continuum
- Chronic Pain or foreseeable need for opioid analgesia
- Pregnant or planning pregnancy
- Recent Overdose or high risk for overdose behavior
- Medical and Psychiatric Co-occurring Disorders
- Diversion Risk
- Additional substance use disorders
- Alternatives

60

60

**Which endogenous opiate receptor type predominantly influences the development of acute opiate withdrawal symptoms?**

A. Mu opiate receptor
B. Kappa opiate receptor
C. GABA B receptor
D. Serotonin 5HT-2A receptor

61

**Which of the following is the correct order from least to most relative opioid potency?**

A. Morphine, diacetylmorphine, fentanyl, carfentanil
B. Fentanyl, morphine, carfentanil, diacetylmorphine
C. Diacetylmorphine, carfentanil, morphine, fentanyl
D. Morphine, diacetylmorphine, carfentanil, fentanyl

62

**The use of FDA approved formulations of buprenorphine to treat opioid use disorder is authorized by the following federal regulation?**

A. Harrison Narcotics Act
B. Controlled Substances Act
C. Narcotic Addict Treatment Act
D. Drug Addiction Treatment Act

63