MEDICATION ASSISTED TREATMENT (MAT) FOR OPIOID USE DISORDER (OUD)

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DISCLOSURE/CONFLICT OF INTEREST

I, Timothy Atkinson, have no actual or potential conflict of interest in relation to this program.

Disclosures:

- axial Healthcare – Consultant
- Daiichi Sankyo – Advisory Board
- Purdue Pharma – Epidemiology Advisory Board
- Honoraria – ACCP, PAINWeek

OBJECTIVES

- Define the following terms: physical dependence, tolerance, active addiction, and substance abuse
- Describe settings for treatment of opioid use disorder and why the U.S. approach is unique compared to other countries
- List available medications to treat OUD and summarize advantages and disadvantages of each medication
- Discuss strategies to manage withdrawal and perform routine monitoring for patients with OUD

STATISTICS

- **Drug overdose deaths increased for the 11th consecutive year in 2010**
- **Drug overdose deaths (38,329) outpaced motor vehicle accidents (35,332) as the leading cause of unintentional death**
  - 57.7% were linked to pharmaceuticals
  - 75.2% of pharmaceutical overdoses involved opioids
- **Opioid-related overdose deaths**
  - 1999 – 4,030 deaths
  - 2010 – 16,651 deaths
- **Opioid prescriptions have increased by ~ 400% over same time period**
  - More patients on chronic opioid therapy

JAMA 2013;309(7):657-659.

EPIDEMIOLOGY

Retrospective Cohort Study:

- Half of the events occurred within the first year of opioid prescriptions
- 33% of events occurred between 1-2 years after opioid initiation
- 13% of events occurred between 2-3 years after opioid initiation
- Overall incidence of drug overdose women > men (0.76% vs 0.56%)

Liang Y, Turner B. National Cohort Study of Opioid Analgesic Dose and Risk of Future Hospitalization. *J Hosp Med.* 2015; 10(7):425-431.

EPIDEMIOLOGY

Retrospective Cohort Study:

- 90 day exposure windows
- Unadjusted overdose risk per annum in >100mg MEDD was 1.8%
- There were seven non-fatal overdose events for every fatal overdose event
- Majority of overdose events occurred in those receiving low to moderate doses of opioids
- 50-100mg HR 3.73 (all overdoses) and HR 3.11 (serious overdoses)
- >100mg HR 8.87 (all overdoses) and HR 11.18 (serious overdoses)

Dunn K, Saunders K, Rutter C et al. Overdose and prescribed opioids: Associations among chronic non-cancer pain patients. *Ann Intern Med.* 2010; 152(2):85-92.

EPIDEMIOLOGY TENNESSEE

Case-Control: (Overdose cases matched with data from TN CSMP)

- Prescribers linked to TN Board of Medical Examiners Licensure Data to determine prescriber specialty
- Cases were defined as receiving 1 prescription in last 12 months confirmed on TN CSMD

High Risk defined:

- ≥4 prescribers (1 year period)- 90% of patients < 4 per year [4.3% controls]
- ≥4 pharmacies (1 year period)- 95% of patients < 4 per year[1.7% controls]
- >100 MEDD (23.6%) [1.5% controls]
- **200-400 MEDD 48% more likely to result in overdose; 101-200 MEDD 34% more likely to OD**
- 63.5% of overdose deaths had prescriptions in the TN CSMP
- 54.6% overdose cases had 1 risk factor; 5.9% had all three risk factors.

Gwira Baumblatt J et al. High-Risk Use by Patients Prescribed Opioids for Pain and Its Role in Overdose Deaths. *JAMA.* 2014; 174(5):796-801.

EPIDEMIOLOGY TENNESSEE

A Retrospective Cohort Study:

- CDC analyzed a commercial database (IMS Health)

In 2012, prescribers wrote 82.5 OPR prescriptions per 100 persons in the United States.

- *State rates varied 2.7-fold for OPR*
- ***TN #2 rank** for most prescriptions 142.8 for every 100 persons*
- ***TN #2** rank for high dose opioid prescribing 8.7 for every 100 persons*
- ***TN #4** rank for benzodiazepine prescribing 61.4 for every 100 persons*

- Alabama, Tennessee, and West Virginia were all ≥ 2 SD's above the mean for prescribing both benzodiazepines and opioids.

Paulozzi et al. Variation among states in prescribing of opioid pain relievers and benzodiazepines - United States, 2012. J Safety Res 2014; 51:125-129.

KEY DEFINITIONS

- Physical Dependence
- Tolerance
- Active Addiction
- Recovery
- Substance abuse

https://www.asam.org/docs/default-source/public-policy-statements/1opioid-definitions-consensus-2-011.pdf
https://blog.samhsa.gov/2012/03/23/defintion-of-recovery-updated/#.WzB9eKdKiUk

DSM-5 OUD CRITERIA

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least 2 of the symptoms in the table above, occurring within a 12-month period.

DSM-5 Criteria	
1.	Craving or strong desire or urge to use opioids
2.	Recurrent use in situations that are physically hazardous
3.	Tolerance
4.	Withdrawal (or opioids are taken to relieve or avoid withdrawal)
5.	Using larger amounts of opioids or over a longer period than initially intended
6.	Persisting desire or unable to cut down on or control opioid use
7.	Spending a lot of time to obtain, use, or recover from opioids
8.	Continued opioid use despite persistent or recurrent social or interpersonal problems related to opioids
9.	Continued use despite physical or psychological problems related to opioids
10.	Failure to fulfill obligations at work, school, or home due to use
11.	Activities are given up or reduced because of use

**Tolerance and withdrawal are not criteria for OUD when taking opioid pain medicine as prescribed.

OPIOID USE DISORDER (OUD)

- DSM-I (1952-1968) – "Addiction" is usually symptomatic of a personality disorder.
- DSM-II (1968-1980) – "Addiction" requires evidence of habitual use ... Withdrawal symptoms are not the only evidence of dependence.
- DSM-III (1980-1994) – Essential feature of "Opioid Abuse" .. pattern of pathological use for at least one month ... impairment in social or occupational functioning ... "Opioid Dependence" essential feature tolerance or withdrawal.
- DSM-IV (1994-2000) – "Opioid Dependence" includes ... compulsive, prolonged self-administration of opioid substances ... for no legitimate medical purpose ... doses that are greatly in excess of the amount needed for pain relief.
- **DSM-V (2013-Present) - categories of substance abuse and substance dependence have been eliminated and replaced with an overarching new category of "substance use disorders"—with the specific substance defining the disorder.**
  - **Tolerance and withdrawal that previously defined dependence are normal responses ..**

CASE #1

A 56 year-old white female was admitted for apparent opioid overdose with successful reversal using a home naloxone kit. Due to multiple psychiatric admissions, she is kept for observation.

PMH: HTN, HLD, diabetes, anxiety, Bipolar I, and polysubstance abuse (heroin, cannabis, and tobacco)

EMT Report: Patient denies drug use but can't explain overdose

- **Family reports she uses heroin but has been trying to get clean recently**
  - **TN CSMD Report – No results**

Appearance:

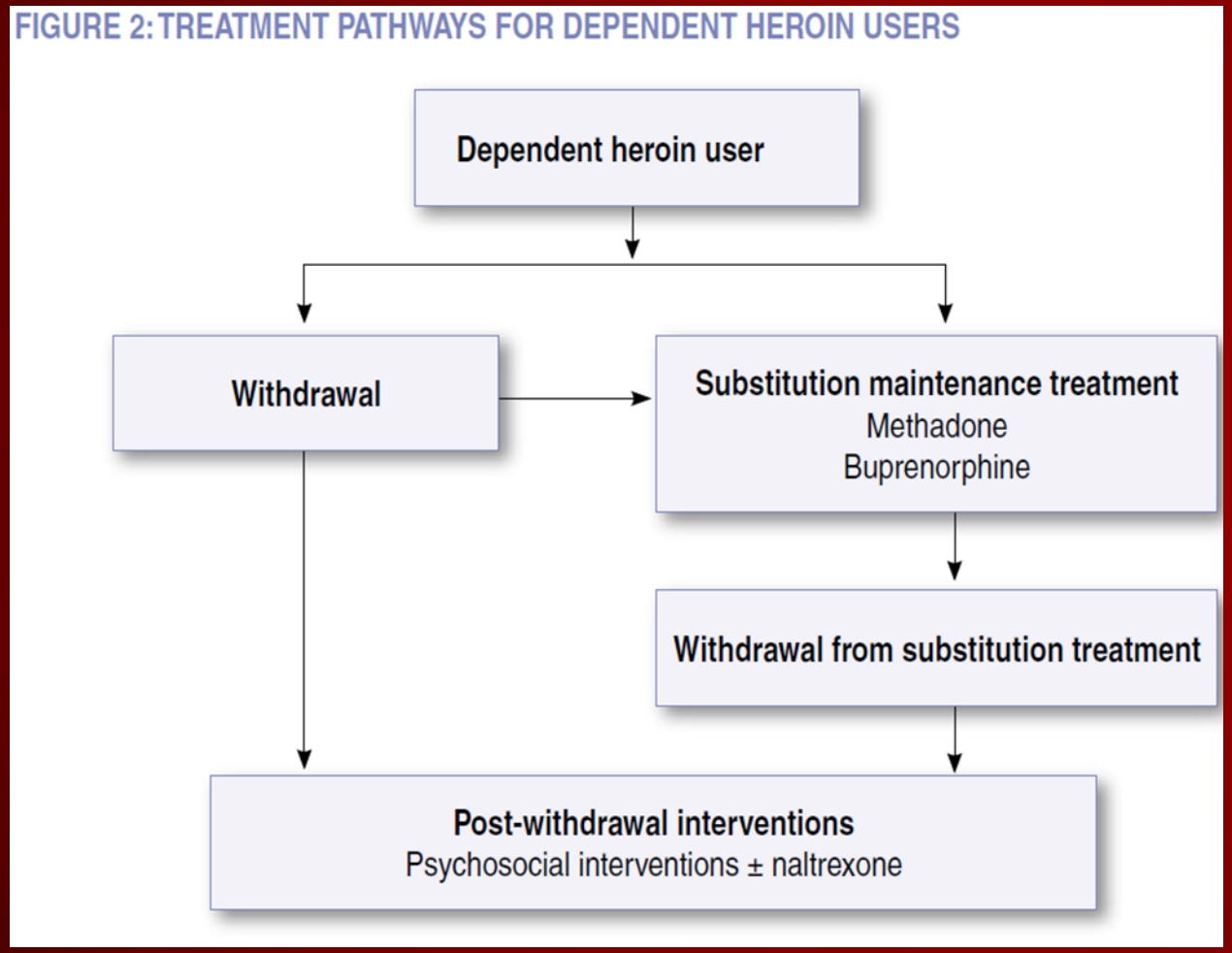
- **Sweating**
- **Fidgety**
- **Very anxious**
- **Crying spells**

Vitals:

- **Heart rate: 110bpm**
- **Dilated pupils**
- **Hair standing on end (piloerection)**

WITHDRAWAL TREATMENT IS NOT AN ENDPOINT

It's a transition of care; so where are we going?



Rx Opioid Withdrawal

- **Reason for withdrawal**
  - Misuse vs lost/stolen meds
- **Patient assessment**
  - Discussion of treatment options
- **Unlikely inpatient without medical complication**
- **Rx opioid overdose**
  - Pathway should look same

Guidelines for management of heroin withdrawal. NationalDrugStrategy.gov

OBJECTIVES FOR HEROIN WITHDRAWAL TREATMENT

Realistic Objectives:

1. Alleviate Distress – Palliation of symptoms
2. Prevent Severe Withdrawal Sequelae
   - Precipitation of acute psychotic episode
   - Wernicke's encephalopathy = dehydration + poor nutrition
3. Enable Engagement and Provide Linkage with Ongoing Treatment
4. To Break a Pattern of Regular and Heavy Drug Use
5. To Get Help with any other Problems

Guidelines for management of heroin withdrawal. NationalDrugStrategy.gov

OPIOID WITHDRAWAL

Symptoms may begin 8-10 hours after last dose

- Half-life ($t_{1/2}$)
- Volume of distribution (Vd)
- Peak in severity 2-4 days after onset

Opioid (IR)	Half-life (h)	Volume of Distribution, L/kg
Codeine	3	3-6
Morphine	2-4	2.7-5.3
Hydrocodone	3.8	3.3-4.7
Oxycodone	3.2	2.6
Hydromorphone	2.5	4
Oxymorphone	2.85-12.79	3
Methadone	8-59	1-8
Fentanyl (IV)	3.65	4
Buprenorphine (SL)	37	430

Ahmed N, Horlacher R, Fudin J. Opioid Withdrawal: A New Look At Medication Options. *Pract Pain Mgmt. Nov 2015; 58-66.*

CLINICAL OPIOID WITHDRAWAL SCALE (COWS)

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

Wesson D, Ling W. Clinical Opioid Withdrawal Scale (COWS). *J Psychoactive Drugs.* 2003; 35(2):253-259.

CLINICAL OPIOID WITHDRAWAL SCALE (COWS)

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 D, Ling W. Clinical Opioid Withdrawal Scale (COWS). *J Psychoactive Drugs.* 2003; 35(2):253-259.

SYMPTOM MANAGEMENT

Opioid Withdrawal is not fatal – Proceed with caution

- Majority managed as outpatient
- Assess severity and need for treatment

Pharmacologic management of symptoms (optional)

- Nausea – Ondansetron, metoclopramide, promethazine
- Diarrhea – Loperamide,
- Anxiety – Betablocker, Benzodiazepine

Treatment recommended in fragile disease states

- History of CAD
- History of psychoses

Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. *J Addict Med. 2015; 9(5):358-367.*

Ahmed N, Horlacher R, Fudin J. Opioid Withdrawal: A New Look At Medication Options. *Pract Pain Mgmt. Nov 2015; 58-66.*

OPIOID WITHDRAWAL

Somatic symptoms result from noradrenergic release

- Blunting NE release is key to treatment
- Many medications have shown evidence for managing somatic symptoms

Alpha-1 Antagonists	Alpha-2 Antagonists	Beta-Adrenergic Antagonists	NMDA Antagonists	Miscellaneous
Prazosin	**Clonidine**	Propranolol	Ketamine	Venlafaxine
Trazodone	Tizanidine	Atenolol	Memantine	Mirtazapine
Phentolamine	Guanfacine		Dextromethorphan	Bupropion
Phenoxy-benzamine	Methyldopa		Amantadine	Haloperidol

Clonidine most often used and recommended (off-label)

- 0.1-0.3mg q6-8 hours (max 1.2mg daily)
- Hypotension (limits use)

Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. *J Addict Med. 2015; 9(5):358-367.*

Ahmed N, Horlacher R, Fudin J. Opioid Withdrawal: A New Look At Medication Options. *Pract Pain Mgmt. Nov 2015; 58-66.*

NALOXONE DISTRIBUTION

Aims to reduce harm and risk of life-threatening opioid-related overdose and deaths among Patients

- Risk factors
  - Loss of tolerance to opioids
  - Mixing opioids with other depressant drugs or alcohol
  - Poor or compromised physical health
  - **I**ncreased risk for opioid overdose

CASE #1 FOLLOW-UP

Our patient was resting comfortably and withdrawal symptoms disappeared after treatment when nurse last checked an hour ago.

As staff enters to discuss discharge plan, the patient appears to be in a stupor and is unresponsive with no noticeable respiration.

A code is called, CPR is initiated and respiration restored. After administration of naloxone, respiration resumes unassisted and patient is transferred to ICU for close supervision.

What happened?

- How long does naloxone last?
- Onset 2 min
- Duration of action: 20-90 minutes

OPIOID OVERDOSE AND TREATMENT

1. Signs of Overdose: (may not all be present)
2. Apnea - ≤ 12 breaths per minute
   - Not in physiologic sleep state
   - Pulmonary edema – later in clinical course
3. Stupor - unresponsive
4. Miosis – pinpoint pupils
   - May appear normal in polysubstance abuse

Naloxone Dosing

Wait 2-3 minutes between steps

Boyer E. Management of Opioid Analgesic Overdose. *NEJM*. 2012; 357(2):146-155.

CASE #1 FOLLOW-UP

The patient has disclosed enrollment in methadone clinic and intent to continue when discharged

- Explains delayed clearance and recurrent overdose

She now has been admitted for over 24 hours and risk of overdose has passed but withdrawal symptoms are persistent

- Treating physician is concerned about protracted withdrawal
- They want to start methadone to alleviate withdrawal symptoms
- Can they do that?

QUESTION

True or False?

It is legal to start methadone for opioid use disorder outside of a registered methadone maintenance clinic?

A. **True**

B. **False**

METHADONE REGULATIONS

- Methadone products used for the treatment of opioid addiction and detoxification or maintenance programs must be: (42 CFR 8.12)
  - Certified opioid treatment program by Mental Health Services (MHS)
  - Approved by the designated state authority
  - Use oral form ONLY

METHADONE REGULATIONS

- <u>Exceptions</u> to certification requirement:
  - During inpatient care, when patient is admitted for any reason **other** than concurrent opioid addiction to facilitate the treatment of the admitting diagnosis (21 CFR 1306.07 (c))
  - During an emergency period of no longer than 3 days **while** definitive care for the addiction is being sought in an appropriately licensed facility (21 CFR 1306.07 (b))

METHADONE REGULATIONS SUMMARY

- Patients can continue methadone for maintenance while inpatient

- Patients can start methadone maintenance therapy while inpatient for 3 days

U.S. UNIQUE APPROACH TO MAT

Two Treatment Settings Available:

1. Outpatient Treatment Program (OTP) [Example: Methadone clinic]

- Most common approach used worldwide
- Intensive treatment program
- Recommended for high risk patients
- Required evaluations with psychiatrist
  - Counseling
- Patients present daily for observed medication administration
- OTP's can offer both methadone & buprenorphine
- Cash ONLY ($12/day)
- May earn right to "carry" or take home medication for a few days

METHADONE FORMULATIONS

- Tablet 5mg, 10mg, 40mg
  - 40mg tablets are detox/maintenance only
- Oral concentrated solution: (10mg/mL)
  - Cherry flavored
  - Sugar-free, no dye, no flavor
- Dispersible tablets: 40mg (forms oral suspension)
- IV solution

MAINTENANCE TREATMENT

- Initial Dosing:
  - 20-30mg/day (max 40mg)
  - Titrate slowly according to withdrawal symptoms
- Typical Maintenance Dose:
  - 80-120mg/day (as a single dose)

PAIN VS MAINTENANCE DOSING

- Maintenance Dosing 40mg - 120mg/day
  - As a single daily dose
- Pain Dosing 5mg - max (opioids have no ceiling)
  - TID dosing is standard
  - BID for liver dysfunction
  - Renal dysfunction – usually not adjusted (very little data)
- Methadone prescriptions scheduled daily are inappropriate for pain
  - BID prescriptions should be scrutinized for appropriateness

METHADONE STATISTICS

- 2% of prescriptions for opioid analgesics are for methadone
- Methadone accounts for nearly 1 in 3 prescription opioid overdose deaths in the U.S.
- 2X times the number of any other opioid

http://www.cdc.gov/features/vitalsigns/methadoneoverdoses/

POTENTIALLY CLINICALLY RELEVANT METHADONE-DRUG INTERACTIONS

Agents That May DECREASE Serum Methadone Concentrations

- Antiepileptics: carbamazepine, Phenobarbital, phenytoin
- Antipsychotics: risperidone
- Antiretrovirals: nevirapine, ritonavir
- Antitubercular: rifampin

Agents That May INCREASE Serum Methadone Concentrations

- Antidepressants: TCA's (amitriptyline)
- Antifungals: fluconazole, ketoconazole, erythromycin

Agents That May Significantly Increase Adverse Effects of Methadone

- Benzodiazepines
- St. John's Wort

OPIOID USE DISORDER

“ … only about half of the public (49%) believes there’s a treatment for prescription-painkiller addiction that’s effective long-term.”

(Blendon, 2018)

	Buprenorphine	Methadone	Naltrexone
Pharmacology:			
Opioid agonist activity	μ, Partial agonist	μ	N/A
Opioid antagonist activity	κ, ϑ	N/A	μ, κ, ϑ
NE reuptake blockade	N/A	✓	N/A
NMDA inhibition	N/A	✓	N/A
Pharmacokinetics:			
Half-life	32-36 hours	15-60 hours	5-10 days
Metabolic pathway	3A4 medicated N-dealkylation to norbuprenorphine and glucuronidation	3A4, 2B6, 2C19 mediated N-demethylation to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP)	6β-naltrexol mediated by dihydrodiol dehydrogenase to glucuronidation
Excretion	Urine (30%) Feces (69%)		Primarily urine
Opioid chemistry	Dehydroxylated phenanthrene	Diphenylheptane	Dehydroxylated phenanthrene
Dosing:	SL, Buccal	PO	IM
PO equivalent dose to 30mg/day of PO morphine	1mg SL	7.5mg PO	N/A
Starting Dose	Up to 8mg	40mg	380mg
Usual Maintenance Dose	8-16mg	80-120mg	380mg

Atkinson T, Fudin J, Pandula A, Mirza M. Medication Pain Management in the Elderly: Unique & Underutilized Analgesic Treatment Options. *Clin Ther.* 2013; 35(11):1669-1689.

U.S. UNIQUE APPROACH TO MAT

Two Treatment Settings Available:

2. Office-Based Outpatient Treatment (OBOT) [Example: Suboxone clinic]

- **DATA 2000 allows physicians to prescribe buprenorphine for OUD in office practice**
  - **24 hours of training, submit waiver notification form, DEA assigns X license #**
  - **1st year 30 patients**
  - **NOI- Request increase to 100 patients**
- **Comprehensive Addiction Recovery Act (CARA) Effective 7/22/2016**
  - **Section 303- authorizes NPs & Pas to obtain waiver for DEA X license**
- **42 CFR Part A (**RIN 0930-AA22)-HHS Rule Effective 8/6/2016
  - **Increase to 275 patients**

Establishing Care in Opioid Use Disorder

US Office-Based Outpatient Treatment (OBOT)

Provider Action	ASAM	SAMHSA	VA/DoD	FSMB
Past Medical History and Physical Assessment	Comprehensive medical history: physical exam, evaluate for infectious diseases, pregnancy, lab tests	Comprehensive assessment: Physical exam; complete history; conditions related to drug abuse, lab tests	History and physical exam, lab tests	Physical exam; thorough medical history; communicable diseases, UDT, PDMP
Mental Health Assessment	Psychiatric stability Psychiatric disorders	Mental status examination Formal psychiatric assessment (if indicated)	Mental Status examination Psychiatric stability Psychiatric disorders	Psychiatric history Psychiatric disorders Readiness to participate in Tx
Substance Use History	Confirm OUD Diagnosis Substance abuse history	Confirm OUD diagnosis; screen for drug or alcohol-related disorders	Confirm OUD Diagnosis; Treatment should be offered for each SUD	Confirm OUD Diagnosis; Use of other substances Past treatment experience
Social History	Identify barriers to recovery: living situation, financial concerns, social support	Social support, family history, readiness to change.	Assess psychosocial functioning and environment	Access to social supports, family, friends, housing, employment, finances and legal problems
Psychosocial Assessment	Assessment of psychosocial needs Medications but one aspect of treatment	Needs assessment; incorporate plan for engaging in psychosocial interventions into treatment plan	Needs Assessment Supportive counseling Referral to community services	Baseline Assessment; Level of psychological and social functioning or impairment
Patient Selection	OBOT vs OTP consider: • Psychosocial situation • Co-occurring disorders • Treatment retention vs risk of diversion Active use of other drugs, associated with poorer prognosis. Not a reason to deny Tx	OBOT: • Reasonable compliance • Motivation & desire Tx • History of stable treatment • Psychosocial supports • Psychiatric stability • Adequate treatment resources • Comorbid substance abuse	OBOT vs OTP: • Patient preference • Stable patients • Provide needed resources • None/few failed attempts at Tx Difficulty accessing OTP	OBOT: • Ability to offer/refer for psychosocial services • Readiness to change • May be candidates even with previous failures
Agreement	Informed consent	Informed consent; treatment plan; provider and patient sign	Not specified	Treatment agreement and informed consent should be signed by patient

ASAM, American Society of Addiction Medicine; SAMHSA, Substance Abuse and Mental Health Services Administration; VA/DoD, Veteran's Affairs/Department of Defense; FSMB, Federation of State Medical Boards; WHO, World Health Organization; MAT, Medication Assisted Treatment; Tx, Treatment; OBOT, Office-Based Outpatient Treatment; OUD, Opioid Use Disorder.

BUPRENORPHINE FOR EVERYONE!

Traditional opioid prescribing is declining

- DEA announced mandatory 25% reduction in production from pharmaceutical companies
- Result of decreased prescribing

Buprenorphine Prescribing is Increasing

Opioid Use Disorder (OUD)

- Probuphine® (5/26/16)
- Bunavail® (6/6/2014)
- Zubsolv® (7/3/2013)
- Suboxone®
  - Sublingual tablet (10/8/2002)
  - Buccal Film (8/30/2010)

Chronic Pain

- Belbuca® (10/13/2015)
- Butrans® (6/30/2010)

Buprenorphine the New Standard

Table Equianalgesic Dose Comparison of Approved Buprenorphine Products

Brand	Generic	Parental (IV)	Oral/Sublingual (PO/SL)	Route of Administration	Formulation	Approved Strengths (mg)
Various+	Morphine	10	30	IV/PO	Solution, Tablet	10-100
Opioid Use Disorder (OUD)						
Suboxone	Buprenorphine/Naloxone	NA	1	SL, Buccal	Tablet, Film¥	2-12
Subutex	Buprenorphine	NA	1	SL	Tablet	2, 8
Bunavail	Buprenorphine	NA	0.53**	Buccal	Film	2.1-6.3
Zubsolv	Buprenorphine/Naloxone	NA	0.7	SL	Tablet	0.7-11.4
Probuphine	Buprenorphine	10§	NA	Subdermal	Implant	80mg
Pain						
Buprenex	Buprenorphine	0.3	NA	IV	Solution	0.3
Butrans	Buprenorphine	NA	15mcg/hr*	Transdermal	Patch	5-20
Belbuca	Buprenorphine	NA	0.6	Buccal	Tablet	0.075-0.9

+Morphine has numerous brand names; *Transdermal dosage form, assumes accurate absorption, high interpatient variability observed; **Dosage form does not exist, equianalgesic dose extrapolated from known equivalence of higher doses; ¥Suboxone film is available as 4mg & 12mg but not in SL tablets; §Dosage form does not exist, equianalgesic dose extrapolated from known equivalence of approved dose for subdermal implant.

BUPRENORPHINE

Receptor activation:

- μ-opioid agonist – partial
- κ-opioid antagonist
- δ-opioid antagonist

Receptor Kinetics:

- Highest affinity of all opioids
- Slow receptor association (30min)
- Very slow receptor dissociation (166min)

Receptor saturation:

- 2mg SL tablet – 36-50% saturation
- 16mg SL tablet – 79-95% saturation

Pharmacology:

- Semi-synthetic derivative of thebaine
- 20-40 times more potent than morphine

Reversal:

- 2-3 times more potent at displacing fentanyl
- 40 times dose of naloxone required to reverse buprenorphine compared to fentanyl

Elimination half-life:

- Single administration – 25hrs
- Multiple administrations – 32-36hrs

Patient Follow-up and Monitoring in Opioid Use Disorder

US Office-Based Outpatient Treatment (OBOT)

Provider Action	ASAM	SAMHSA	VA/DoD	FSMB
Visit frequency	Frequently during initiation (at least weekly); stable patients (at least monthly)	Frequently during induction, stabilization. Weekly, biweekly, or monthly depending on stability.	Twice weekly, then weekly, then biweekly up to 12 weeks	Frequently until stable; follow-up frequency based on compliance and high risk behaviors
Duration	No time limit Taper/discontinuation is a slow process and requires careful consideration of factors including: • Treatment engagement • Patient stability • Patient preference • Improved social support	Maintenance can be short-term (1 year) up to lifetime Duration depends on patient: • Stability • Preference	No time limit Longer durations (>90 days) associated with improved outcomes	Recommend at least a year; Longer duration associated with better outcomes Relapse risk is highest in first 6-12 months of abstinence
Prescription Frequency	Weekly or monthly	Weekly or monthly	Not specified	As needed until next visit, Coincides with follow-up based on compliance and high risk behaviors
Usual Dosing	8-16mg daily FDA limits at 24mg daily No evidence at higher doses but increased diversion risk Divide dose for comorbid pain diagnosis	Nearly all patients will stabilize on daily doses of 16–24 mg; some, however, may require up to 32 mg daily.	12-16mg Moderate evidence higher dosing is more effective Divide daily dose for concurrent chronic pain	8-24mg; some may require up to 32mg daily.
UDT	Baseline; Frequently; Random preferred	Baseline; At least monthly	Baseline; Frequent; at provider discretion	Baseline; Routinely; Recommended and included in treatment agreement
Pill counts	Unscheduled recall visits	Not specified	Not specified	Recommended and included in treatment agreement
PDMP	Verify abstinence	Not specified	Not specified	Baseline; Routinely; Recommended to verify abstinence and included in treatment agreement

Urine Drug Testing Methods[3-5]		
Type of Test	Logistics	Pearls
Initial Screening Test: Immunoassay	• Inexpensive • Fast • Widely available	• High sensitivity, low specificity (higher potential for false positives) • Opiate screen not sensitive for semisynthetic (e.g. oxycodone) or synthetic opioids (e.g. fentanyl)
Confirmatory Test: Gas chromatography-mass spectrometry (GCMS)+ or Liquid chromatography-mass spectrometry (LCMS)	• Expensive • Time consuming	• High sensitivity, high specificity • Expensive • Detects medication even if concentration is low

+ GCMS is considered the criterion standard for confirmatory testing; Immunoassay tests have high predictive values for marijuana and cocaine, but lower predictive values for opiates and amphetamines

Critical to understand lab tests at your facility

<u>UDS Samples are saved for X days</u>

Initial Screening (Immunoassay)→ [Same day]

Confirmation test → Send out lab (LC-MS) [7-10 days]

STANDARD OPIATE IMMUNOASSAY SCREEN

Morphine	**300 ng/mL**
Hydrocodone	**1,700 ng/mL**
Hydromorphone	**1,700 ng/mL**
Oxycodone	**23,000 ng/mL**
Oxymorphone	**41,000 ng/mL**

MANAGING UNEXPECTED RESULTS

Decide in advance how you will handle these different scenarios:

- Negative for prescribed medications
- Positive for non-prescribed medications
- Positive for illicit substances

TOP 10 ABNORMAL UDS PATIENT RESPONSES

10. “I haven't ever taken methamphetamines, that's speed isn't it? First it was marijuana, that I didn't take, now it’s methamphetamines, so what is it gonna be next?”

9. “I don’t take my medicine in the morning before our appointments because I refuse to drive impaired”

8. “Someone sabotaged me…again.”

7. “They put my urine sample next to 10 others on a table without any labels, they must have mixed it up”

6. “Wow….Really??.....maybe my marijuana was laced with cocaine?”

TOP 10 ABNORMAL UDS PATIENT RESPONSES

5. “They must have given me cocaine in the ER, then! Do they do that?”

4. “I keep a pill bottle filled with urine in my sock because….it’s sometimes hard to go on demand!”

3. “I was positive for cocaine because my girlfriend uses it and I’m positive because we were intimate”

2. “My body processes the drugs differently and they often don’t show up in UDS. My old doctor was aware, if you call him, he’ll tell you.”

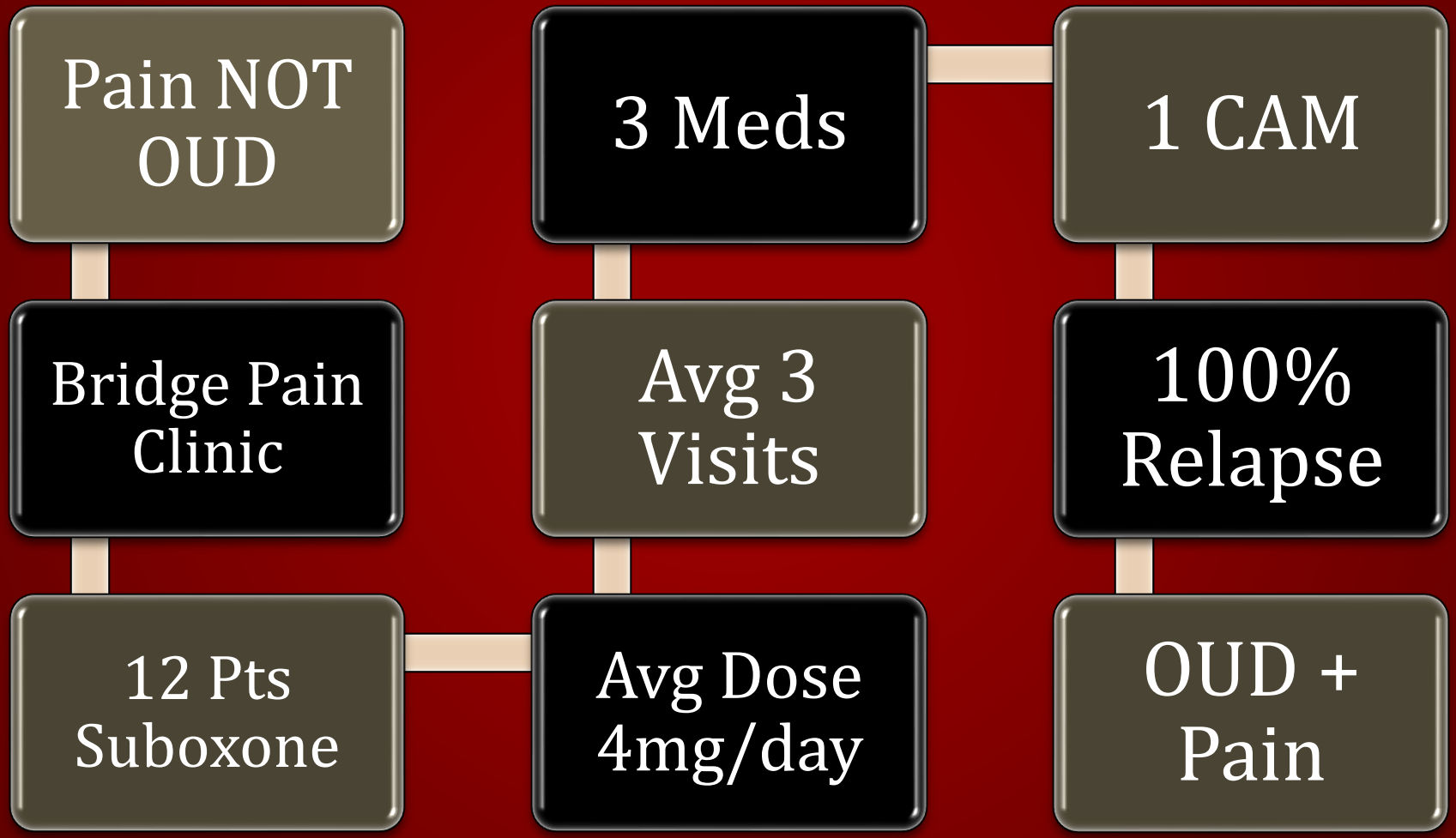
1. “That son of a @#%! sold me dirty urine!”

Psychosocial Interventions and Care Coordination in Opioid Use Disorder

US Office-Based Outpatient Treatment (OBOT)

Provider Action	ASAM	SAMHSA	VA/DoD	FSMB
High Risk (OBOT questionable)	Alcohol use disorder Benzodiazepine use Suicidal/Homicidal Ideation May not be suitable for OBOT: • Alcohol Use Disorder • Sedative, hypnotic, anxiolytic use disorder • High risk of diversion • Stimulant, cannabis, and other drugs not reason to deny treatment.	Alcohol abuse/dependence Benzodiazepine or sedative/hypnotic abuse/dependence Suicidal/Homicidal Significant untreated psychiatric comorbidity Frequent relapses or multiple failed treatments Poor motivation or psychosocial support	Pain requiring IR opioids Many failed attempts at treatment	• Use of sedatives or alcohol • Continue to misuse and experience withdrawal at 32mg daily • Persistent aberrant behaviors despite adjustments to treatment
Psychosocial Treatment	Recommended for every patient on MAT Individual, couples and/or group counseling; Cognitive Behavioral Therapy (CBT) Contingency Management (CM) Relapse prevention Motivational Interviewing Mutual Help – not equivalent to professional psychosocial Tx	Necessary for most patients on MAT • Improved outcomes with higher levels of psychosocial support Counseling, group or individual; self-help groups Self-help groups may be beneficial, but many do not accept MAT patients • Formal therapy may have better outcomes	No treatment can be recommended over another Behavioral Couples Therapy Cognitive Behavioral Therapy (CBT) Contingency Management (CM) Community Reinforcement Approach (CRA) Individual Counseling Motivational Enhancement Therapy 12-Step Facilitation Recommended and effective with participation	Recommended for patients on MAT; Evidence that MAT + psychosocial superior to either alone. Regular assessment of patient's level of engagement in treatment • Counseling • 12-Step Facilitation
Care Coordination **Case Management**	Linkages to existing family support systems Referrals to community-based services: • Employment • Housing • Legal	Providers should be aware of available community services Consider referral to social workers or case managers for services: • Employment • Family • Legal	Social and environmental factors can impact recovery if note addressed Access to supportive recovery environment: • Housing and social support • Employment • Legal	Develop recovery support system Assess changes in social functioning and relationships • Family/friends • Employment • Housing • Legal
Relapse	Increase treatment intensity Increase/change psychosocial supports	Plan should be in place for relapse in treatment agreement; Physicians should be familiar with Brief Intervention: • Assess relapse triggers • Social & Recovery Environment • Insight, motivation, and readiness to change	Adapt treatment to meet patient needs Add or substitute another psychosocial or medication intervention Change intensity with med or therapy adjustments	Reassess treatment plan; intensify structure and/or intensity of services • Assess and develop coping skills • Identify and plan for relapse triggers

IS IT REALLY OUD IF PATIENT HAS PAIN?



BRIEF INTERVENTION

- Initially studied to reduce problematic alcohol use
- Highly effective
- Validated in several studies
- Numerous variations available
- Now recommended for all substance use disorders
- Easily adapted and effective when discussing opioids

1. Miller WR, Sanchez VC. Motivating young adults for treatment and lifestyle change. In: Howard, G. (ed.) Issues in Alcohol Use and Misuse in Young Adults. Notre Dame, IN: University of Notre Dame Press, 1993.
2. Grossberg PM, Brown DD, Fleming MF. Brief physician advice for high-risk drinking among young adults. Annals of Family Medicine 2004;2:474-480.

FRAMES

Feedback of Personal Risk	• Express concern for potential medical problems
Responsibility of the Patient	• Opioid use is a choice
Advice to Change	• Incorporate adjunct therapies
Menu of Alternative Strategies	• Educate on alternative treatments
Empathetic Counseling	• More effective than confrontation
Self-Efficacy	• Provide encouragement to achieve goals

THANK YOU!

QUESTIONS?