Update on Opioid Use Disorders

Joshua Blum MD

No Disclosures

Learning Objectives

- Utilize DSM-5 criteria to diagnose opioid use disorder
- Implement rational opioid weaning protocols and withdrawal treatment
- Counsel patients regarding OUD treatment options
- Make effective referrals to treatment based on severity of disease and ASAM placement criteria
- Recognize newly emerging treatment formulations

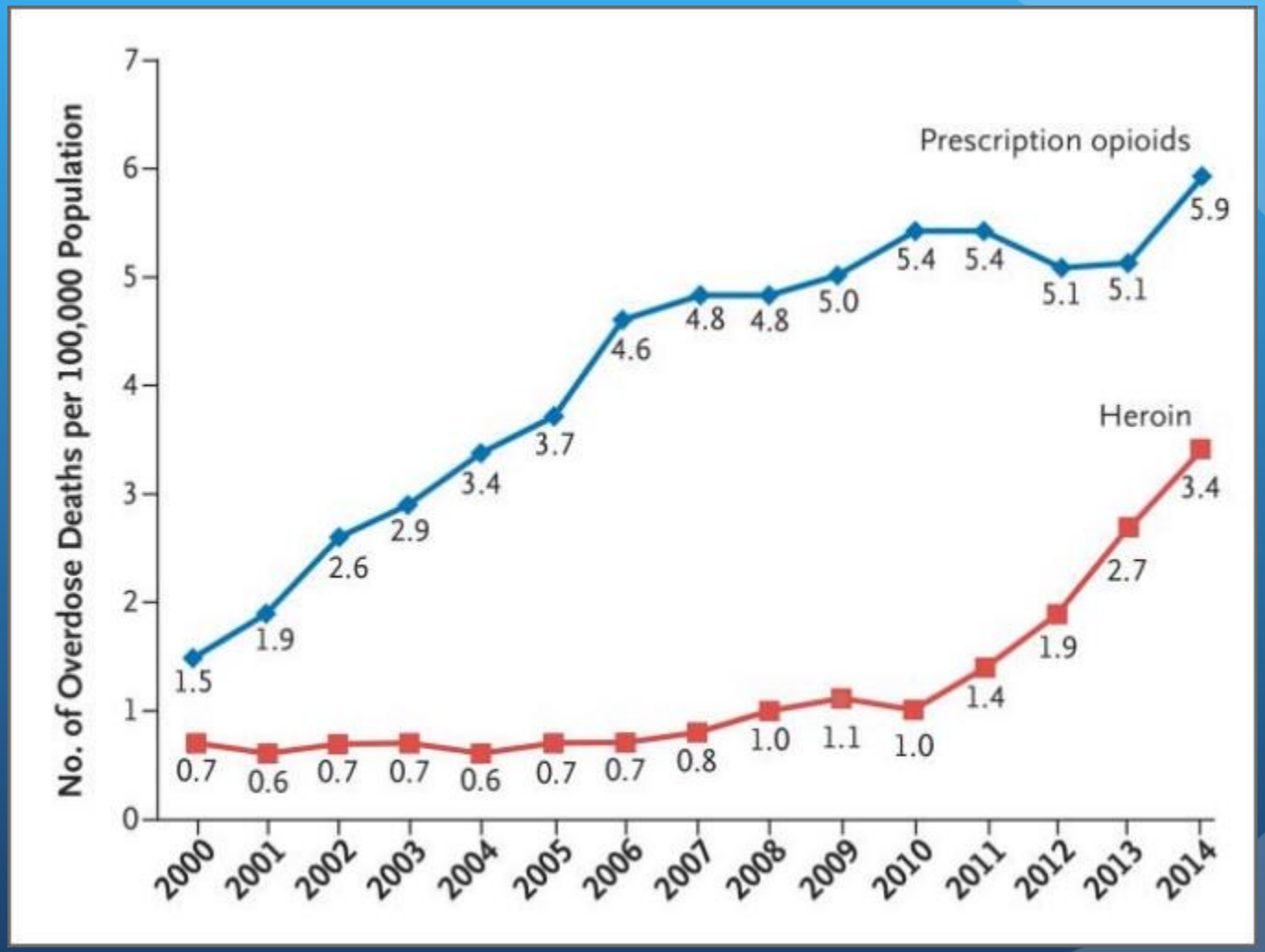
Case 2

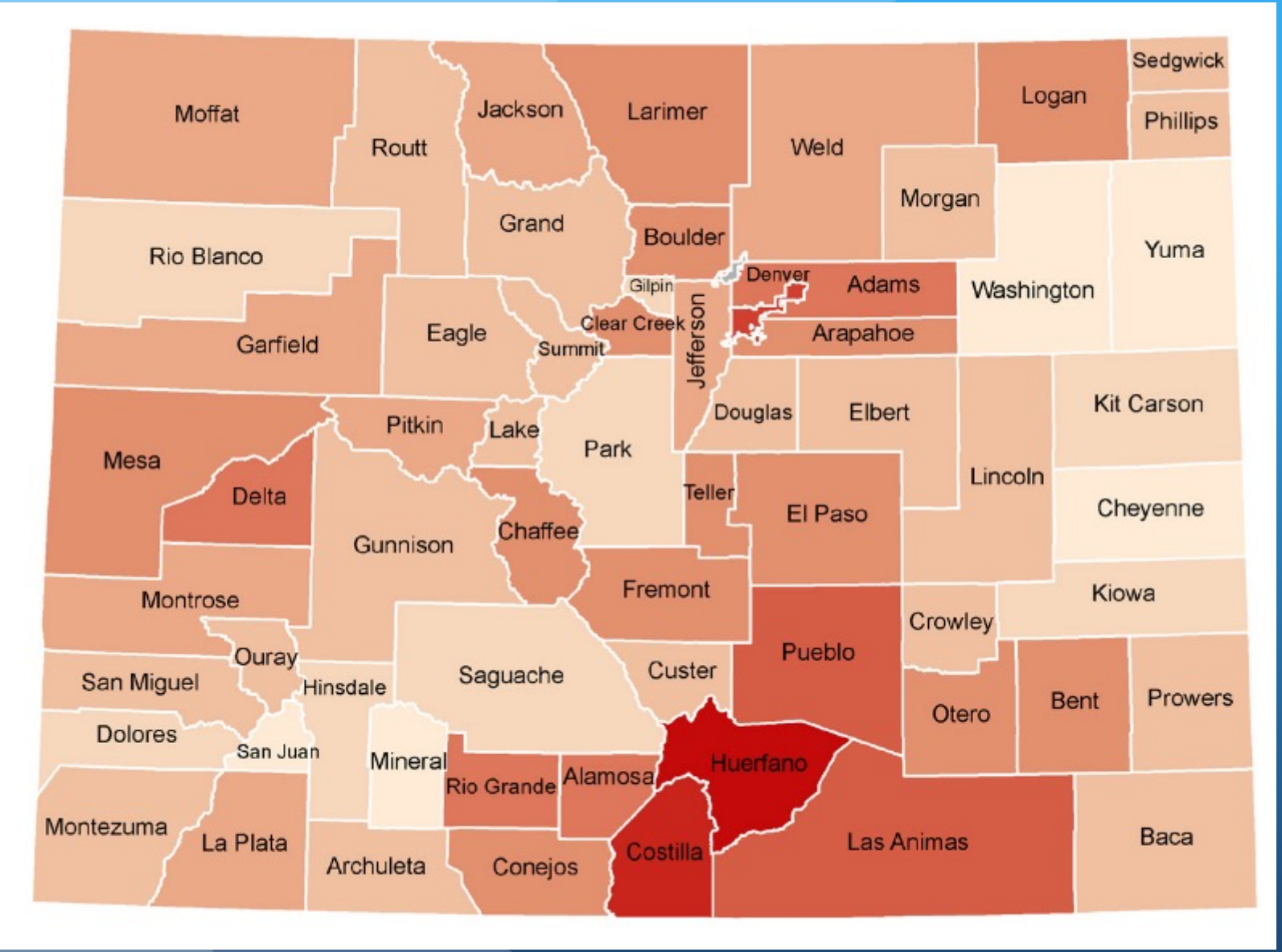
55 y.o. female with long history of multiple chronic pain syndromes, long history of chronic opioid therapy. and frequent ED visits for pain control, multiple office calls demanding early medication refills and escalating behavior. Very defensive and blames others when questioned about opioid use, including denying prior aberrant behaviors. History of depression and suicide attempts, also poly-substance abuse in past. History of heroin abuse, later on methadone maintenance ("but I got over that years ago"). Urine toxicology tests intermittently positive for cocaine.

Why do we care about appropriate diagnosis and treatment of opioid use disorders?

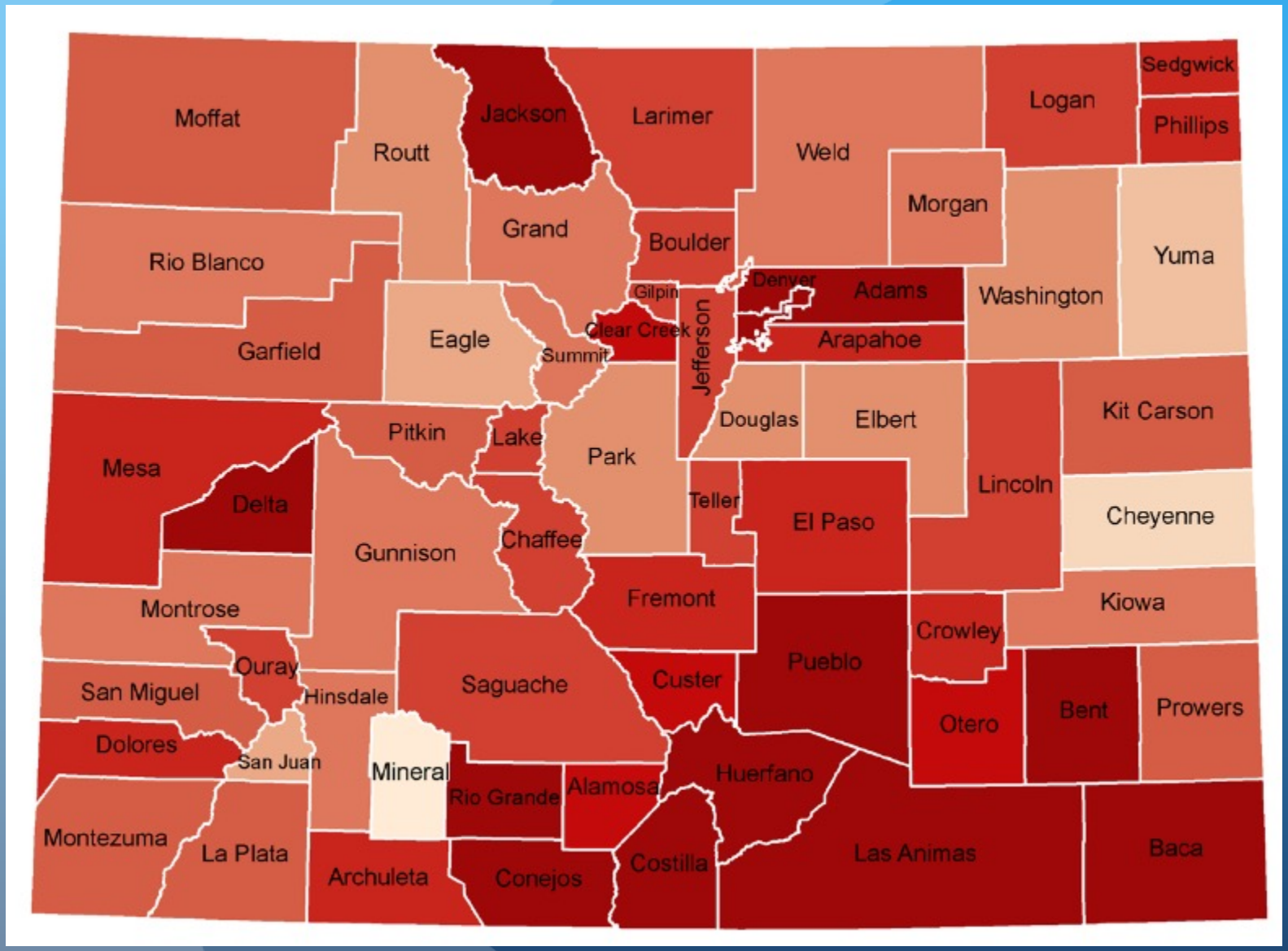
- National and local opioid overdose epidemic
- Opioid discontinuation ≠ treatment
- Medical standard of care
- Legal risk

Overdose death rates: U.S.





Colorado Counties: Overdose death rates: 2002



Colorado Counties: Overdose death rates: 2014

Maybe things are starting to improve in Colorado

OPIOID OVERDOSE DEATHS

2015	2016
472	442

- Prescription opioids account for the decrease
- Greatest decreases with oxycodone, hydrocodone

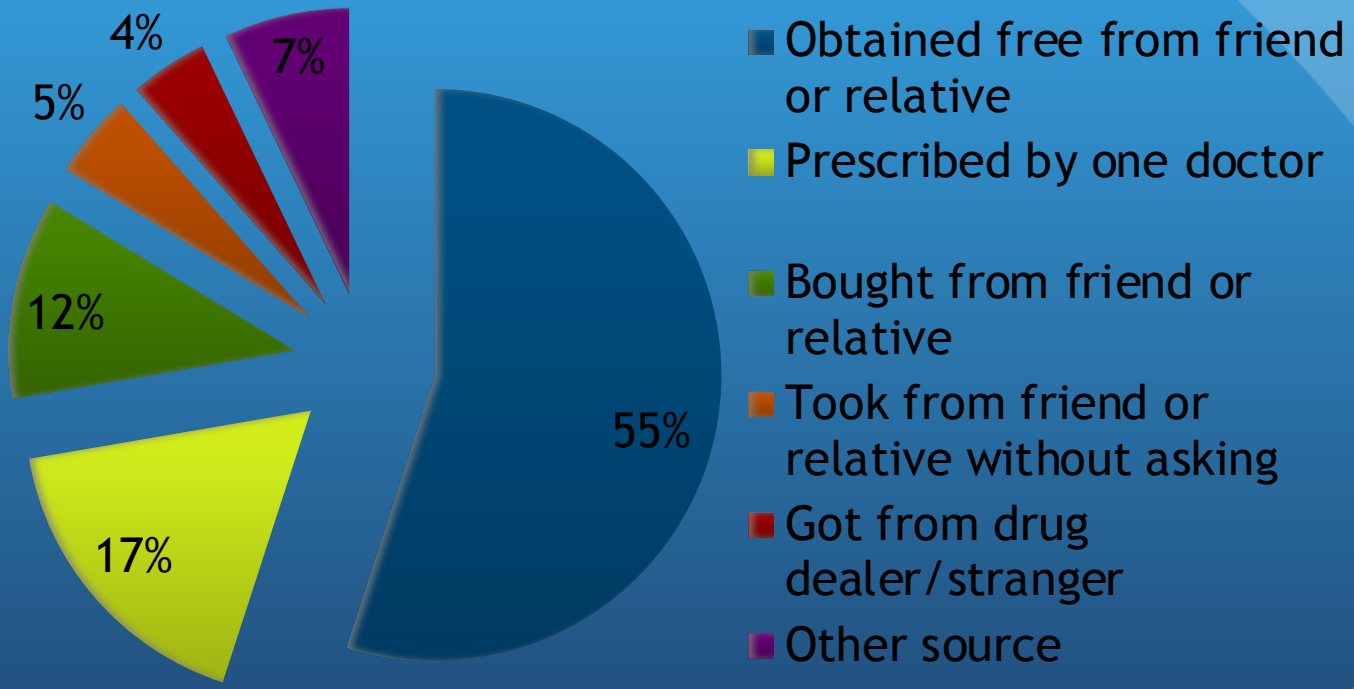
Unfortunately the news isn't good for heroin

HEROIN OVERDOSE DEATHS

2015	2016
167	197

- Most heroin users initiate use with prescription opioids

Sources of diverted opioids



Medical standard of care

- CDC and most other recent guidelines recommend identification of OUDs and referral to appropriate treatment

Medicolegal

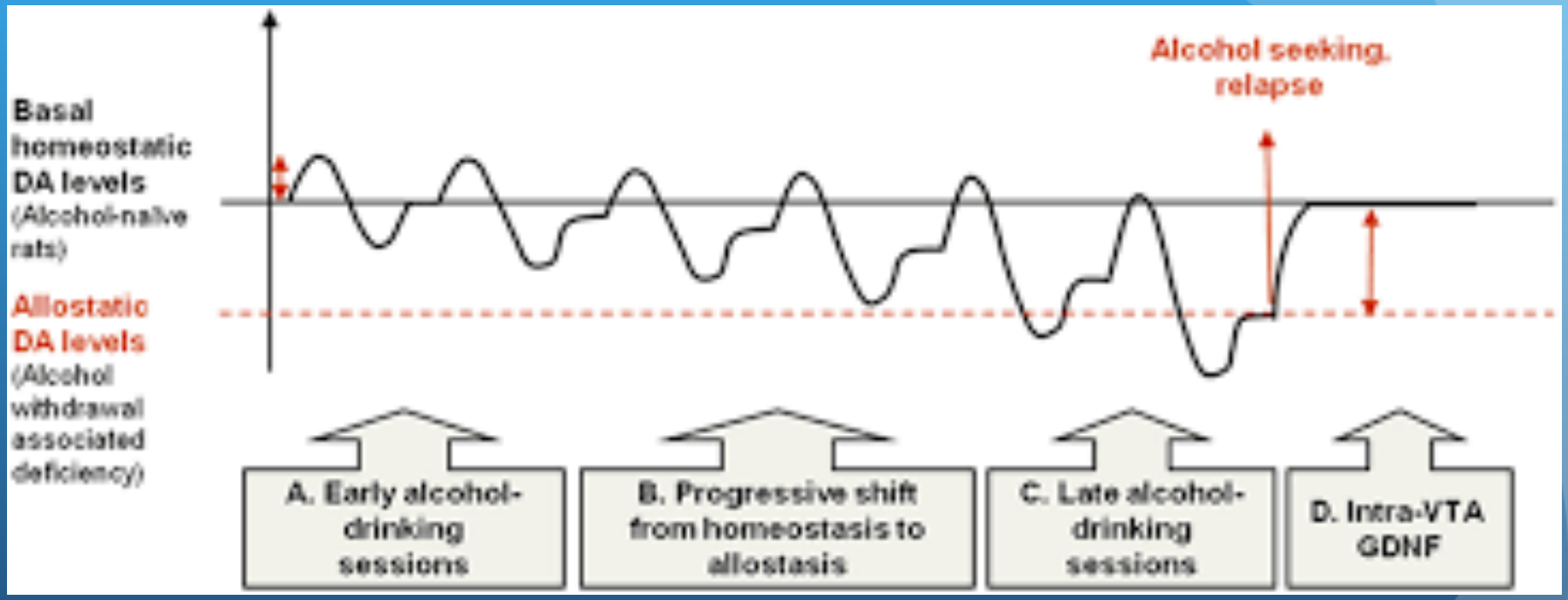
- Unintentional overdose a source of significant liability and potential investigation
- Greater sophistication among prosecutors
- Civil liability an inadequate deterrent
- Severity of charges:
  - Involuntary manslaughter: high-risk activity without due caution
  - Second-degree murder: indifference to consequence

Troxel DB *REMS: Opioid-related patient safety and liability.* The Doctors Company 2012
Barnes MC Trends in Law and Policy Affecting Opioid Prescribing. Presented ICOO June 2013

COT produces irreversible changes

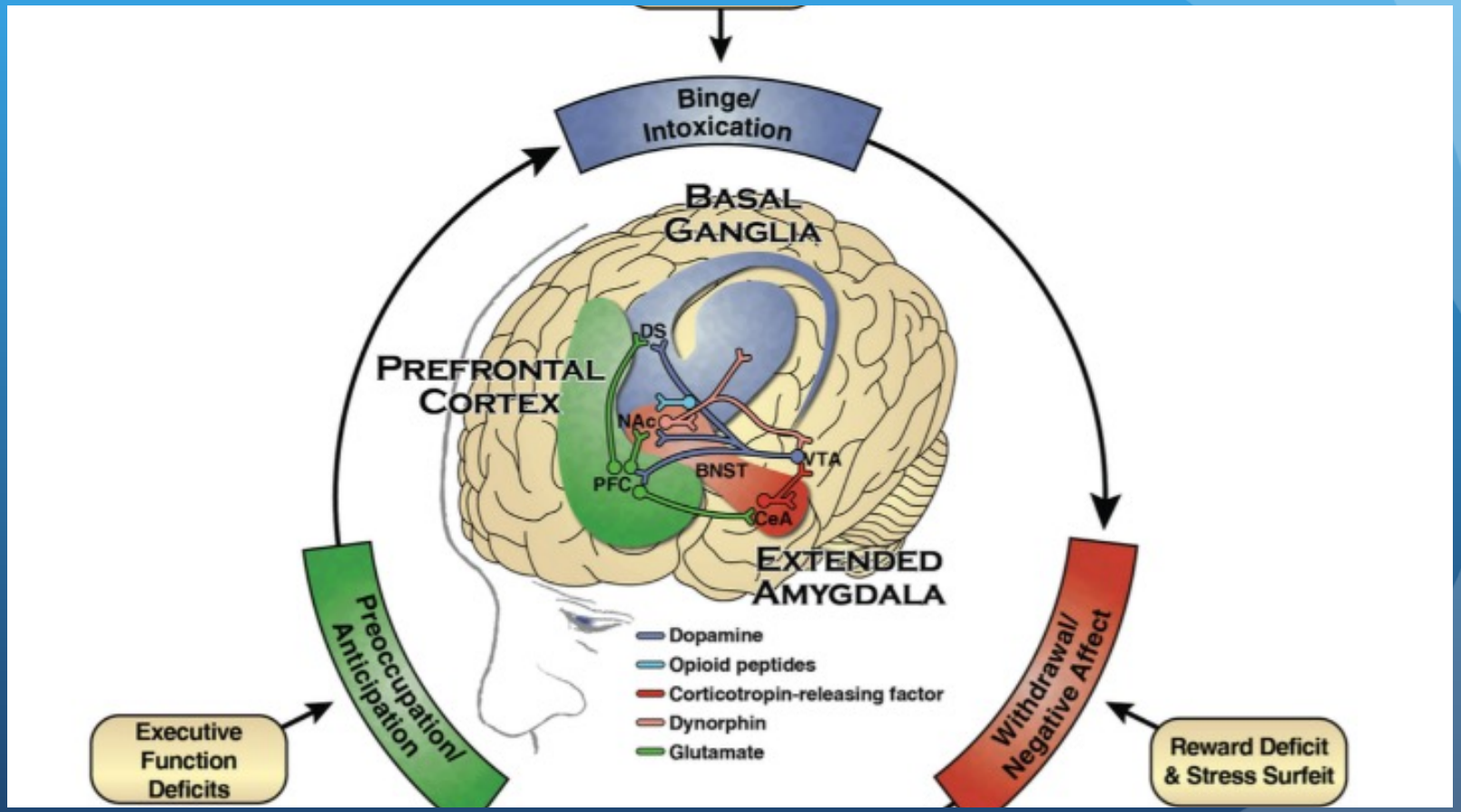
- Mu receptor mediates opioid effects high affinity for enkephalins, beta endorphins, and opioids
- •Dose dependent changes Repeated exposure to short acting opioids
  - Neuronal cellular and receptor adaptations Mesolimbic dopamine system
- Mediate tolerance, withdrawal, craving, self-administration
- Explain chronic and relapsing nature of opioid use disorder
- Basis of pharmacotherapies to stabilize neuronal changes

Dopamine and addiction

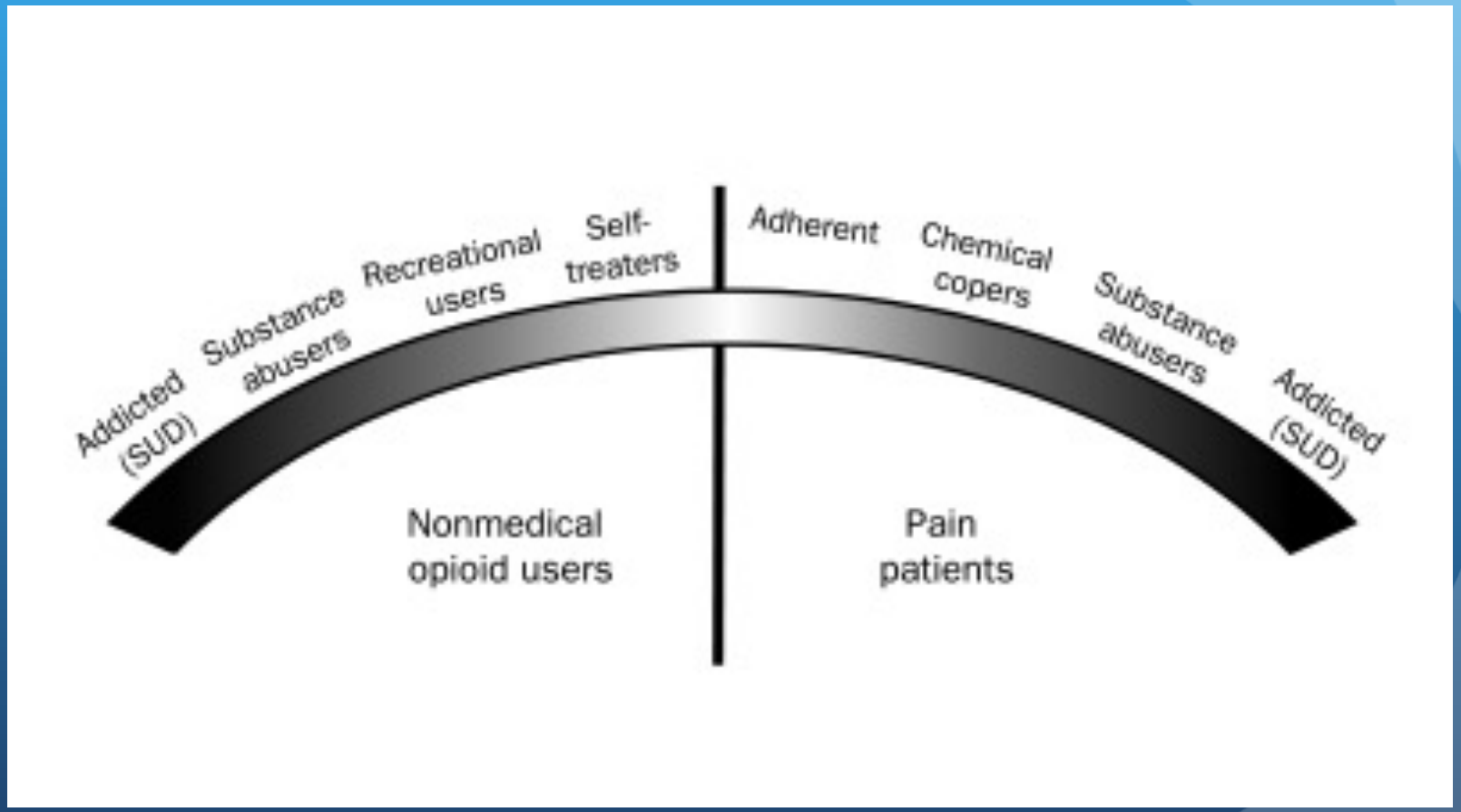


□□□□,2003

Addiction cycle



Spectrum of opioid user subtypes



Passik SD Mayo Clin Proc. 2009;84:593-601

Watch out for the “chemical coper”

- Term first coined in palliative care setting
- Tendency to somatize everything
- Alexythymia
- Excessive focus on drugs
- May be on a large number of centrally acting medications
- Unmotivated for non-drug therapies
- Less severe signs of abuse might never trigger addiction referral

Passik SD Mayo Clin Proc. 2009;84:593-601

Clinical inertia

- Cohort of patients (N 9,009) without “abuse” diagnoses prior to prescribing who later have these diagnoses
- Prescribing to patients with documented drug abuse infrequently change prescribing habits

Paulozzi, L. Changes in the medical management of patients on opioid analgesics following a diagnosis of substance abuse. Pharmacoepidemiology and drug safety. May 2016

Convincing yourself and the patient that he/she has an opioid use disorder

OUD Diagnosis: DSM-V

- No more “abuse” or “dependence”
- Addiction = Dependence = Substance Use Disorder
  - Mild: 2-3
  - Moderate: 4-6
  - Severe: ≥7

Diagnosis

- Using more/longer than intended
- Unsuccessful efforts to quit/cut down
- Lots of time spent getting, taking, recovering from drug use
- Craving

LOSS OF CONTROL

- Giving up activities because of use
- Use despite negative effects/consequences
- Failure to fulfill major roles (home/school/work)
- Using when physically unsafe
- Continued use despite physical or psychological problem

CONSEQUENCES

- Tolerance*
- Withdrawal*

PHYSICAL DEPENDENCE

The real conversation isn't spoken

Side effects
Constipation
Sedation
Time Management
Inconvenience
Writing Rxs
Frequent follow up
Toxicology test
License censure
RISK OF DEATH
ADDICTION
DIVERSION

How's your pain today?

TERRIBLE!

WITHDRAWAL
Side effects
INCONVENIENCE
INSOMNIA
ANXIETY
$
PAIN
MY meds

Setting boundaries and having the difficult conversation

- A few potential strategies:
  - Invoke “do no harm”
  - Build discrepancy
  - Commiserate with the patient
  - Explain your risk and your duty to other patients and society
- Patients will disagree, and may get very angry
  - May need to validate your actions by calling attention to your rights and expertise as a physician
  - Describe addiction as a medical disease rather than a personal failing or character defect

Further techniques

- Evoking change: building discrepancy
  - “I hear you say that you’re tired of being in so much pain, that you don’t have much energy, and that the medications don’t work very well, despite the fact that you are taking extra and running out early. Help me understand how continuing your current regimen is going to help you?”

Most important: offer reassurance!

- “Many patients who come off of opioids notice that their pain actually improves and that they have more energy.”
- “We will taper your medications very slowly in order to prevent withdrawal.”
- “I look forward to seeing you frequently and will do everything else possible to treat your pain aggressively.”

Should you fire patients who violate contracts?

"The surest way to hurt patients (and society) is to abandon them when they deviate from the constructive relationship envisaged by the treating practitioner, only to trail from physician to physician to obtain the drug they need, or worse still, seek illicit supplies."

Ballantyne JC, Opioids for Chronic Nonterminal Pain, Southern Medical Journal 2006

Where to treat: ASAM Placement Criteria

- Latest revision released 2001
- Clinically-driven approach
- Goal is to establish the least intensive level that can safely accomplish treatment
- Not fixed; may be fluid for an individual patient
- 12-step and other recovery groups, spirituality excluded from levels

ASAM Patient Placement Criteria

1. Acute intoxication/withdrawal severity potential
2. Biomedical conditions and complications
3. Emotional, behavioral, and cognitive conditions
4. Readiness for change
5. Relapse, continued use, or continued problem potential
6. Recovery environment

1. Acute intoxication/severity of withdrawal

- Assess the need for withdrawal management:
  - Is there a serious history of withdrawal?
  - Is the patient having similar symptoms again?
  - Does the patient need to be hospitalized?

2. Biomedical conditions and complications

- Co-occurring physical health conditions:
  - Does the patient have severe, uncontrolled cardiovascular, gastrointestinal, hepatic, renal, or neurologic conditions that are not related to intoxication/withdrawal?

3. Emotional, behavioral or cognitive conditions or complications

- Co-occurring diagnosed or undiagnosed mental health conditions
- Complications that may distract the patient from addiction treatment
- Dual diagnosis requires coordination with mental health treatment services
  - Is the patient an imminent harm to self or others?
  - Does the patient struggle to function with ADLs?

4. Readiness to change

- Use motivational enhancement techniques to improve patient motivation
  - Is patient feeling ambivalent?
  - Does he/she feel treatment unnecessary?
  - Does he/she blame others?
  - Has he or she been coerced or is required to have treatment?

5. Relapse, continued use or continued problem potential

- Assess readiness for relapse prevention services and encourage as appropriate

6. Recovery environment

- Assess need for housing, financial, family, legal, or transportation support
  - Is there a dangerous family/living/work situation threatening the patient's safety?

Treatment levels of service

Level	Name	Detox description
0.5	Early intervention	N/A
I	Outpatient	Mild withdrawal; daily or less supervision; likely to complete detox and continue treatment
II	Intensive Outpatient Partial Hospitalization	Moderate withdrawal with all-day or 24 hour support; likely to complete detox
III	Residential: may be low, medium, or high intensity Inpatient: medically monitored	Severe withdrawal; 24-hour nursing/medical care needed; unlikely to complete detox without monitoring
IV	Medically-managed/intensive inpatient	Severe, unstable withdrawal; 24-hour medical care needed to manage medical instability

How can pain experts use the ASAM criteria?

- Identify uncomplicated patients at low risk for severe complications who may be appropriate for SUD treatment in primary care
- This population may be considered for clinic-based MAT with buprenorphine or naloxone

OUD treatment: Detoxification

Acute opioid withdrawal

- Near mirror opposite of agonist effects
- Acute symptoms peak in 24-48 hours
- Slowly decrease over 3-5 days for short-acting opioids
- May last 10 days or longer if patient on long-acting opioids
- Subacute withdrawal syndrome often follows
  - Anhedonia, fatigue, insomnia
  - May last months

Kosten TR, O'Connor PG. N Engl J Med 2003;348:1786-1795

Opioid withdrawal: risks

- Rarely fatal
- Can worsen medical conditions
  - Blood pressure
  - Glycemic control
- Can worsen psychiatric disease
  - Hypomania
  - Psychosis
  - Disorientation

Opioid detoxification: candidate selection

- Maintenance treatment not available
- Maintenance treatment not wanted or no longer wanted
- Detoxification alone associated with high rates of relapse

Predictors of detox failure

- History of multiple relapses with tapers
- Forced tapers
- Short duration of abstinence
- Uncontrolled comorbid substance use disorders
- Unstable social situation
- Pregnancy

Opioid detoxification: gradual

- **Substitute short-acting agonist with long-acting agonist or partial agonist, then taper slowly**
- Methadone:
  - Start at equianalgesic methadone dose and taper over ≤30 days
- Buprenorphine:
  - Initiate after withdrawal symptoms begin
  - Tight receptor binding
  - Start 2-4 mg
  - Titrate to 4-16 mg/day until withdrawal symptoms cease
  - Taper off over 7-14 days

Is one agent superior to another?

- Cochrane review
- 23 controlled trials / nearly 2500 subjects
- Methadone compared with buprenorphine, LAAM, alpha agonists, anxiolytics
- Differences in side effects but not in completion rates
- Methadone superior to placebo in 2 studies
  - Less severe withdrawal symptoms
  - Lower drop-out rates

Amato L et al. Cochrane Database Syst Rev 2013;2:CD003409

Opioid detoxification: rapid

- Clonidine is a mainstay
  - α-2 agonist
  - Reduces central and peripheral sympathetic activity
  - Good for sympathetic arousal only
  - Disadvantages:
    - Doesn’t treat central dysphoria
    - Dose titration necessary
    - Hypotension, dry mouth

Opioid detoxification: multiple meds often required

- Anxiety
  - Benzodiazepines
  - Antihistamines
- Insomnia
  - Trazodone
  - Zolpidem
- Other drugs
  - Gabapentin
  - Tizanidine
- Body aches
  - NSAIDs
  - Anti-spasmodics
- Nausea/vomiting
  - Neuroleptics
  - 5-HT3 antagonists
- Diarrhea
  - Anti-diarrheals

Sample regimen

Drug	Sig	Comments
Clonidine	0.1 mg Q4 hours x 2-3 days	Taper over 1 week
Ondansetron	8 mg BID	
Loperamide	2 mg 4 times/day	Reports of abuse
Gabapentin	600 mg BID	
Ibuprofen	600 mg every 6 hrs	Hold for dehydration
Trazodone	50-100 mg QHS	

Opioid detoxification: ultra-rapid

- Involves naloxone administration under heavy sedation or general anesthesia
- Not associated with better outcomes than slower, less invasive approaches
- Associated with adverse events
  - Aspiration pneumonia
  - Pulmonary edema
  - Ketoacidosis

Maintenance of abstinence: Antagonist Therapy

Opioid antagonists

- Naltrexone
  - Oral
  - Parenteral

Naltrexone

- Competitive antagonist at μ- and κ-opioid receptors, and to a lesser extent at δ-opioid receptor
- Blocks opioid effects
- Not associated itself with tolerance, withdrawal, or abuse potential
- Decreases likelihood of relapse

Gonzalez JP, Brogden RN. Drugs 1988;25:192-213

Naltrexone rationale

- Extinction: patients will stop use if you block the pleasurable effect
- Craving goes away when opioids aren't available
- Decreased cue-induced craving and priming

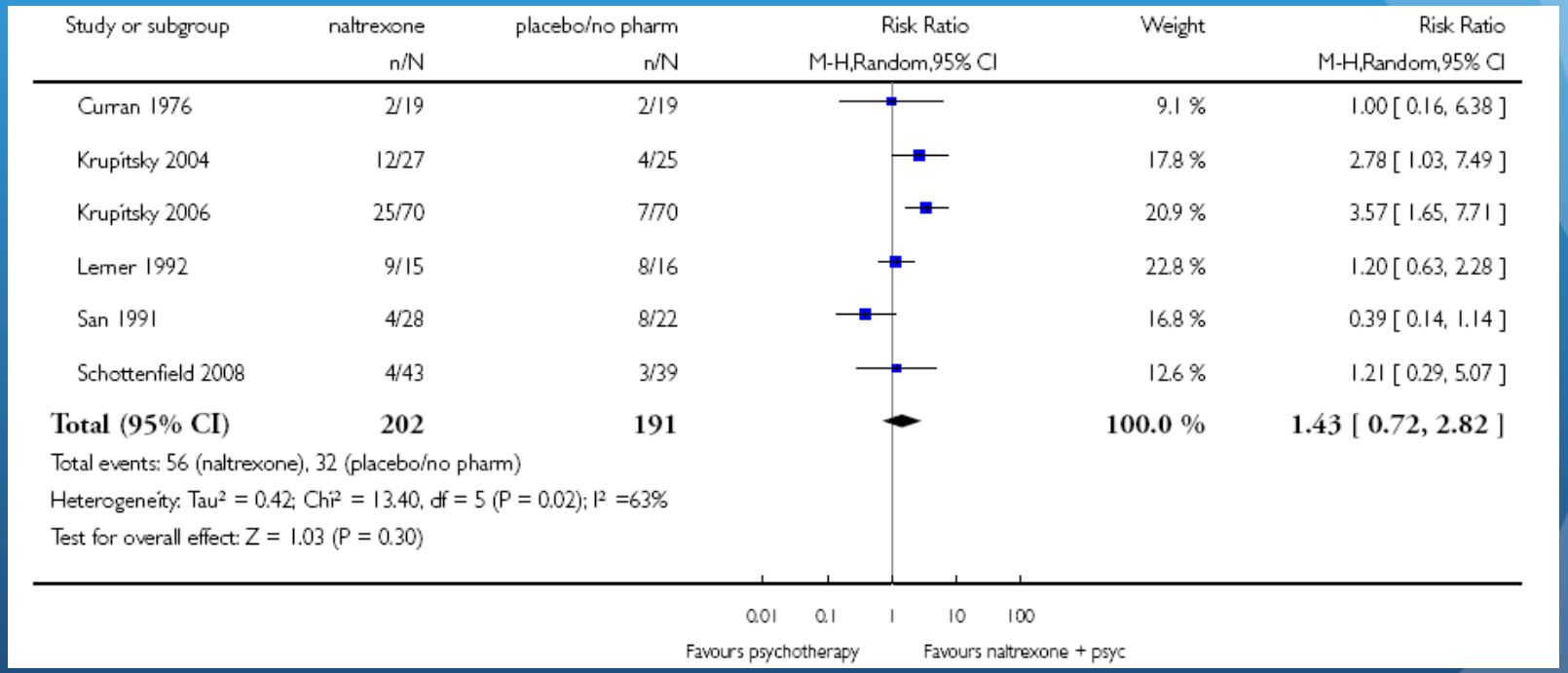
Predictors of success with naltrexone maintenance

- Older age
- Stable family relationships
- Absence of psychiatric disease
- Lower level physiologic dependence
- Shorter duration of opioid dependence

Oral naltrexone

- Oral formulations limited by tolerability of induction and poor adherence
- Cochrane review concluded that oral naltrexone not better than placebo in:
  - Retention in treatment
  - Use of primary substance
  - Side effects
- May still have use in specific populations:
  - Healthcare professionals
  - Employed with stable social contacts

Oral Naltrexone vs. Placebo



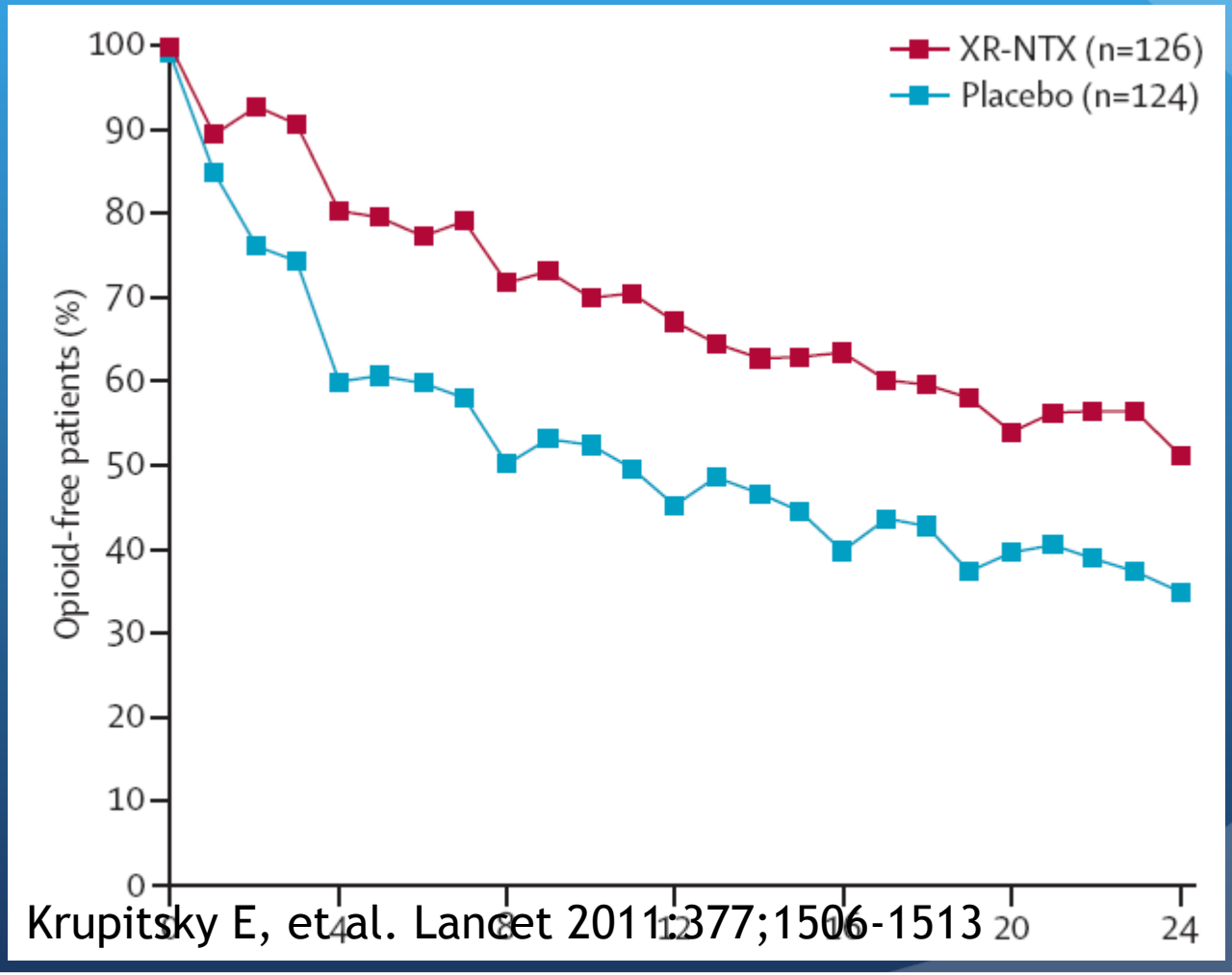
Minozzi et al. *Cochrane Database of Systematic Reviews* 2011

Naltrexone IM

- Approved 2010
- Weeks of abstinence 90% in treatment arm vs. 35% in placebo group
- 99.2% vs. 60.4% opioid-free days
- Much less craving
- Median retention 168 vs. 96 days

Krupitsky E, et al. Lancet 2011:377;1506-1513

Naltrexone IM



Krupitsky E, et al. Lancet 2011;377;1506-1513

Naltrexone: other forms

- Also formulated as an implant
- 52.9% of treatment patients vs. 15.7% of oral naltrexone or placebo patients still in treatment at 6 months
- Replaced every several months
- Used for years in Australia
- Not yet FDA approved: FDA declined 4/30/13, requesting more data

Krupitsky E, et al. Arch Gen Psychiatry 2012;69:973-981

Naltrexone induction strategies

- Treat patient through detoxification phase
- Begin 7-10 days after last opioid use
- Consider bridging with oral naltrexone to prevent relapse: 1-7 days
- Begin injection

Maintenance of abstinence: Agonist Therapy

Advantages of opioid maintenance

- Reduced illicit drug use
- Reduced euphoria
- Decreased consequences from opioid use
  - HIV infection
  - HCV infection
  - Overdose
  - Criminal behavior

Advantages of opioid maintenance

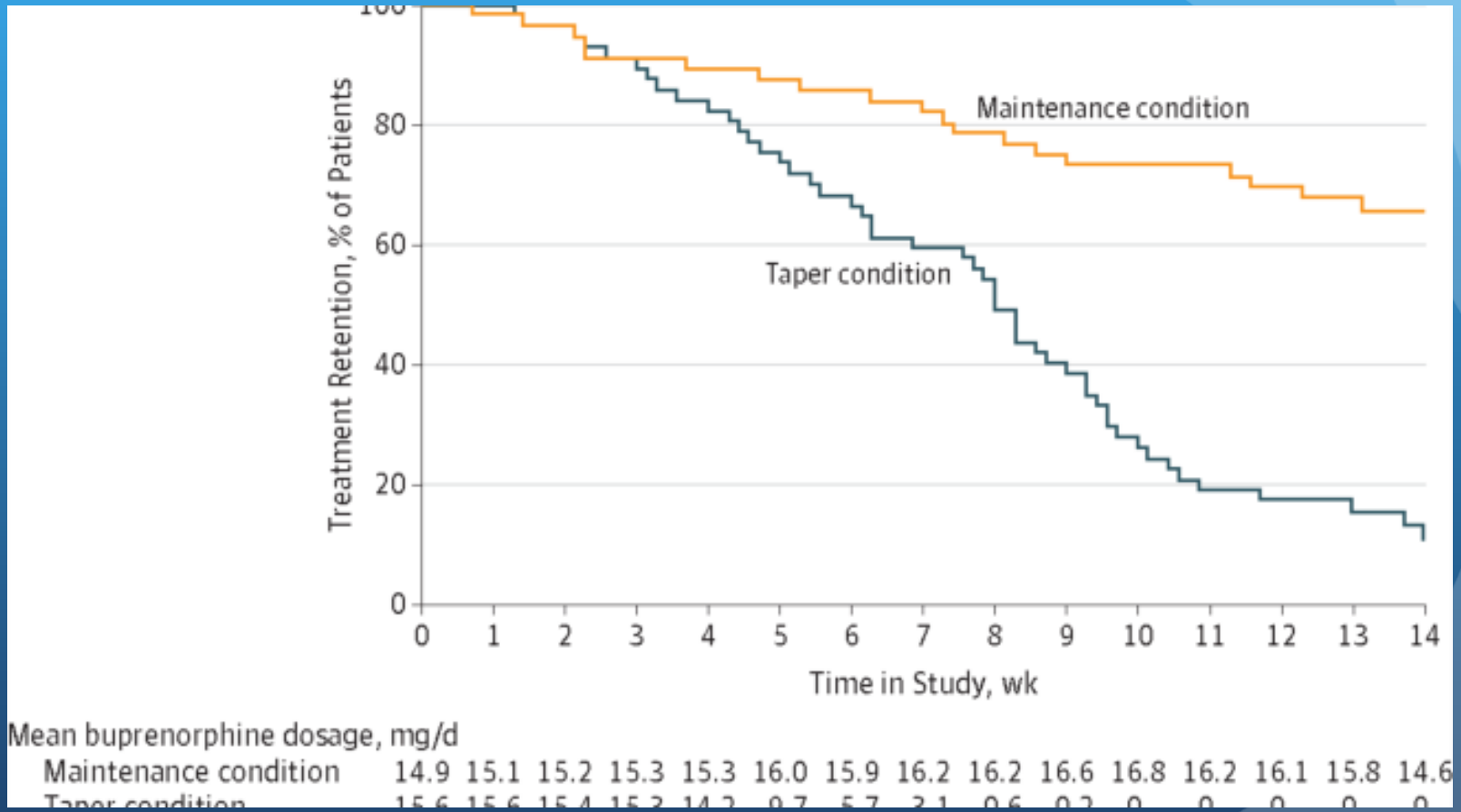
- Opioid detoxification is difficult!
- Depression and anxiety disorders common among opioid users
  - Buprenorphine and other opioids have significant psychoactive properties
    - Anti-anxiety
    - Anti-psychotic
  - Difficult to distinguish between withdrawal-mediated anxiety/dysphoria vs. underlying psychiatric sx uncovered during drug withdrawal

Buprenorphine/naloxone

- Naloxone not absorbed when used sublingually
- Usual effective dose 8-24 mg daily
- Maintenance phase:
  - Physician visits
  - Urine toxicology testing
  - Discussion of relapse prevention and trigger avoidance
- Side effects: headache, constipation, transaminitis
- Contraindicated in pregnancy

Renner JA, Levonuis P, ed. Handbook of office-based buprenorphine treatment of opioid dependence

Detoxification vs. maintenance



Mean buprenorphine dosage, mg/d

Maintenance condition	14.9	15.1	15.2	15.3	15.3	16.0	15.9	16.2	16.2	16.6	16.8	16.2	16.1	15.8	14.6
Taper condition	15.6	15.6	15.4	15.3	14.2	9.7	5.7	3.1	0.6	0.2	0	0	0	0	0

Fiellin D et al. JAMA Intern Med. 2014;174(12):1947-1954.

Conclusion:

- Multiple studies have consistently demonstrated better outcomes when patients receive MAT
  - Decreased drug use
  - Better retention in care
  - Decreased risk of death

Opioid maintenance options

Medication	Action	Usual effective dose	Freq	Adverse effects
Methadone	Agonist	20-150 mg orally	Daily	Constipation, respiratory depression, dizziness, sedation, diaphoresis, drug interactions
Buprenorphine	Partial agonist	8-24 mg sublingual	Daily-3x/wk	Constipation, headache
Buprenorphine /naloxone	Partial agonist plus antagonist	8-24 mg sublingual	Daily-3x/wk	Constipation, headache Contraindicated in pregnancy

Drug Addiction Treatment Act of 2000

- Allows a "waivered" physician to prescribe a DEA Schedule III, IV, or V drug approved for treatment of opioid use disorder in the outpatient setting
  - Buprenorphine products are only drugs approved
- Requires 8 hours of training
- Patient limits:
  - 30 in year 1, 100 in year 2
- Certify capacity to refer the patients for appropriate counseling and other appropriate ancillary services

Not scary!

DATA 2000 Act Update 2016

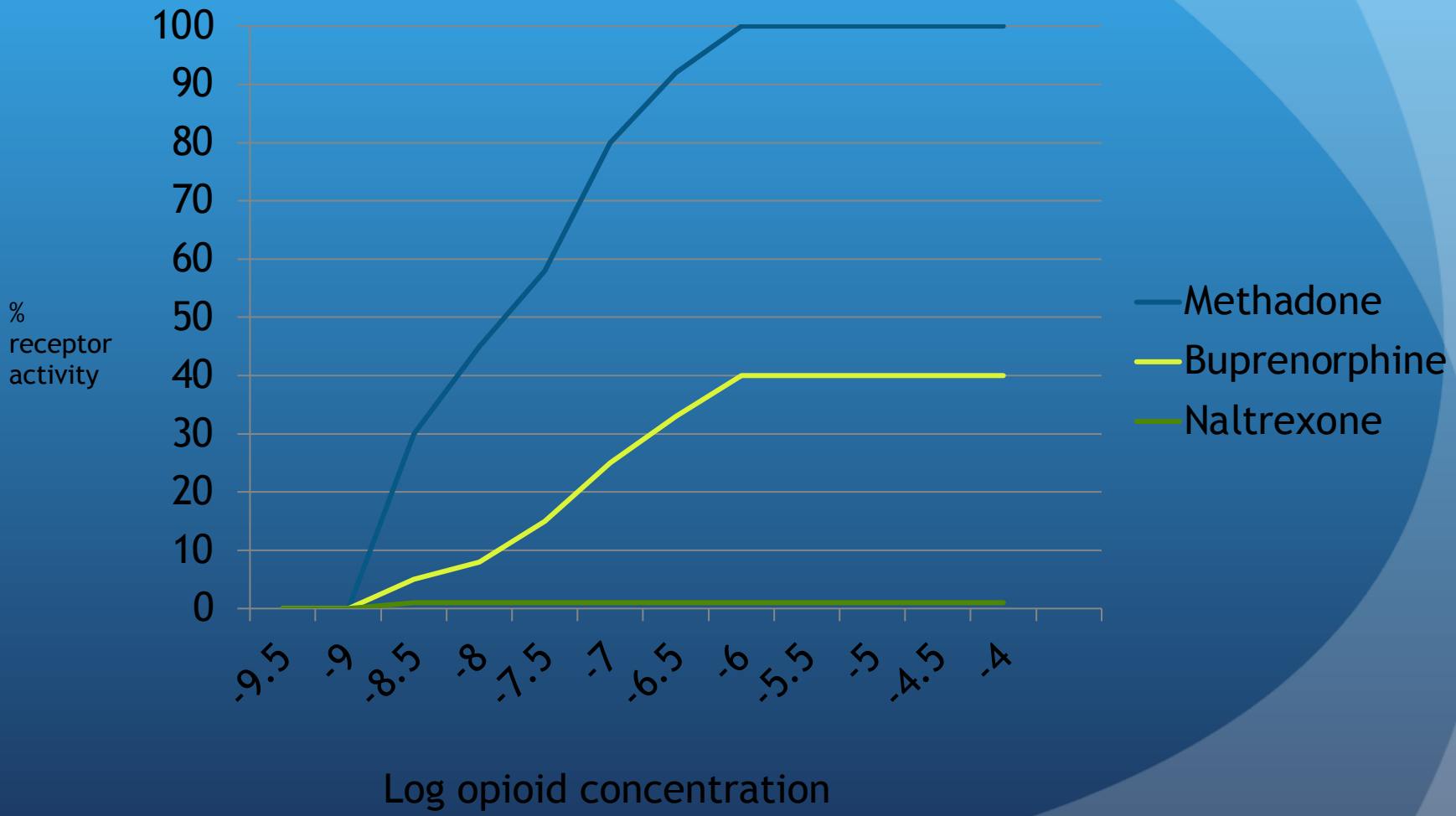
- Nurse Practitioners and Physician Assistants approved to be waivered
  - Requires 24 hours of training

Buprenorphine

- Partial μ-opioid agonist
  - *Ceiling effect*
  - *Long half-life*: 24-42 hours
  - *Strong receptor affinity*

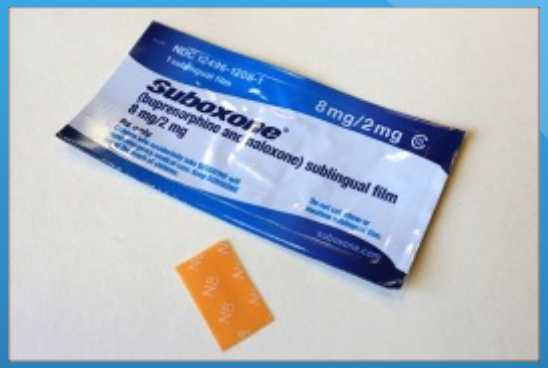
  - DEA Schedule III

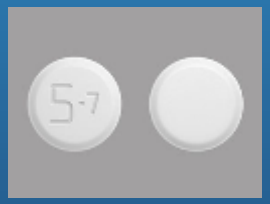
Mu opioid receptor activity

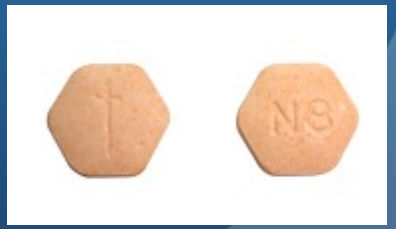


Buprenorphine + Naloxone

- Naloxone added to prevent misuse
- Prevents parenteral use
- Buprenorphine monotherapy used in pregnancy







Buprenorphine induction

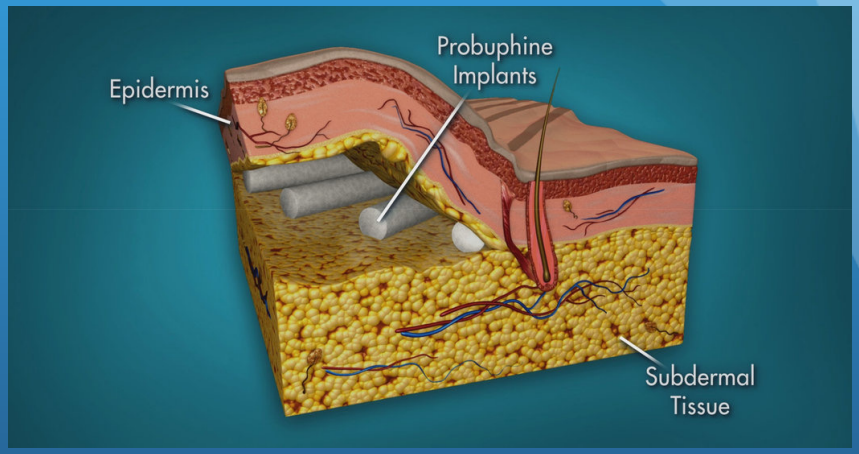
- Patient must be in opioid withdrawal
  - Last dose of short-acting:12-16 hours
  - Last dose of long-acting: 24-36 hours
- Use a scale to determine withdrawal
  - Clinical Institute Narcotic Assessment
    - 11-item questionnaire combines self-report with observations
  - Clinical Opioid Withdrawal Scale
    - Includes BP and pupil diameter
  - Subjective Opioid Withdrawal Scale

Buprenorphine: other forms

- Implant: Probuphine
- Depot injection: RBP-6000

Buprenorphine implant

- Appropriate for stable patients on buprenorphine tablets or films at dose of ≤8 mg/day
- REMS program
  - Training required
  - Closed system
- Covered by most insurances



RBP-6000: Depot injection

- 300 mg buprenorphine in a polymeric solution
- Phase 3 study completed late 2016
- Fast-track FDA approval expected this year

- RBP-6000 study patients were new to care rather than stable patients

Maintenance of abstinence: Counseling

How much counseling is required for successful outcomes?

- 27 studies/3124 subjects compared any psychosocial intervention plus maintenance treatment to maintenance treatment alone
- “Adding psychosocial support to standard maintenance treatments do not add additional benefits”

Amato L et al. Cochrane Database Syst Rev 2011;10:CD004147

Does adding opioid drug counseling to standard medical management improve outcomes?

Table 2. Successful Opioid Use Outcome by Counseling Condition (SMM vs SMM+ODC) at 3 Time Points

	Observed, No./Total No. (%) [95% CI]		GEE Model–Based Results	
Time Point	SMM	SMM+ODC	OR (95% CI)[a]	*P* Value
End of phase 1	24/324 (7.4) [4.8-10.8]	19/329 (5.8) [3.5-8.9]	1.3 (0.7-2.4)[b]	.36
Phase 2, end of treatment	84/180 (46.7) [39.2-54.2]	93/180 (51.7) [44.1-59.2]	0.8 (0.5-1.2)[c]	.27
Phase 2, 8-wk posttreatment follow-up	13/180 (7.2) [3.9-12.0]	18/180 (10.0) [6.0-15.3]	0.7 (0.3-1.3)[c]	.22

Abbreviations: GEE, generalized estimating equation; ODC, opioid dependence counseling; OR, odds ratio; SMM, standard medical management.
[a]The reference category is SMM+ODC.
[b]Adjusted for chronic pain at baseline and lifetime history of heroin use.
[c]Adjusted for chronic pain at baseline, lifetime history of heroin use, and phase 1 randomization.

- Standard Medical Management: 45 min. initial, 15 min. follow-up visits
- About 50% response at end of phase 2
- No improvement adding more intensive opioid drug counseling

Weiss RD et al. Arch Gen Psychiatry 2011;68:1238-1246

Study Conclusions

- “Physicians can successfully treat many patients dependent on prescription opioids, with or without chronic pain, using buprenorphine-naloxone with relatively brief weekly medical management visits.”
- “Individual drug counseling did not improve opioid use outcomes when added to weekly medical management visits.”

Weiss RD et al. Arch Gen Psychiatry 2011;68:1238-1246

Increasing treatment capacity in Colorado

- $2.4 million grant to expand training capacity for NPs
  - Establishes new training center at CU
- $500,000 State grant to establish ‘Hub and Spoke’ model in metro and rural areas
- Failure of Obamacare repeal suggests that Medicaid and other insurers will continue to pay for SUD treatment

Suggestions

- Consider adding buprenorphine-waivered provider to pain practices
  - Buprenorphine is an excellent analgesic and can be a great options for patients with pain and OUD
- Establish strong communication and referral relationships with experienced SUD treatment providers
  - Including methadone clinics

Case 2

55 y.o. female with long history of multiple chronic pain syndromes and frequent ED visits for pain control, multiple office calls demanding early medication refills and escalating behavior, despite increasing doses. Now on fentanyl patch 50 mcg/hr and hydromorphone 4 mg Q4h prn. Very defensive and blames others when questioned about opioid use, including denying prior aberrant behaviors. History of depression and suicide attempts, also poly-substance abuse in past. Urine toxicology tests intermittently positive for cocaine. Has been threatening and adversarial to PCP during discussions about possible misuse. No engagement in other forms of pain treatment. Recently lost job because of too many missed days.

Does this patient meet criteria for an opioid use disorder?

Case 2

Criterion	Present/Absent
Taken in larger amounts/longer period than intended?	✓
Desire to cut down or unsuccessful efforts to control use?	✓
Great deal of time spent acquiring/using/recovering?	✓
Craving/strong desire or urge to use?	?
Failure to fulfill major role obligations at work/school/home?	✓
Continued use despite persistent social/personal problems?	? ✓
Important social, occupational, recreational activities lost?	? ✓
Recurrent use where physically hazardous?	N
Recurrent psychological or physical problems caused or exacerbated by drug?	✓
Tolerance	N/A
Withdrawal	N/A

Conclusions

- Don’t ignore evidence of opioid use disorders
- Diagnose OUDs using DSM-5 criteria
- Explain Dx to patients using medical and non-pejorative terminology
- Treat OUDs appropriately
  - Either within your practice or by referral
  - ASAM Placement criteria can be a helpful framework
  - Opioid discontinuation alone is not adequate
- Develop a relationship with local addiction treatment providers and clinics

END

Questions?