Opioid Stewardship and the Pharmacology of Medication Assisted Treatment

MHA Medication Safety Learning and Networking Day
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Disclosures

- I have no financial interests to disclose.

- Some of these slides have been adapted from materials created by:
  - Gavin Bart, MD, PhD (Hennepin Healthcare)
  - Provider's Clinical Services Support (pcssnow.org) buprenorphine waiver training

Learner Objectives

1. Explain rationale supporting each medication for opioid use disorder (MOUD)

2. Discuss safety considerations for each medication

3. Describe analgesic implications of each MOUD

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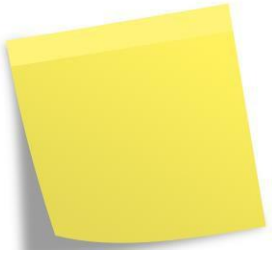
Pharmacology Foundations

8/22/2019

Pharmacology 101: Receptor interaction

- Affinity - strength of drug's physical coupling
  - Not activity at receptor
- Dissociation – speed (slow or fast) that drug uncouples from the receptor
- Efficacy - response to binding (e.g., agonism)
- Potency
  - Amount of drug to produce a given effect
  - A combination of affinity and efficacy



Pharmacology 101: Receptor effect (or not)

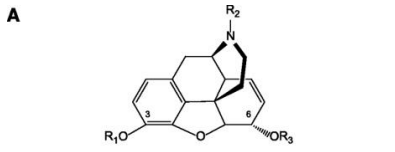
- Agonist
  - Binds and activates receptor
  - Morphine, methadone, fentanyl

- Partial agonist
  - Binds and activates receptor with partial efficacy
  - Buprenorphine, tramadol

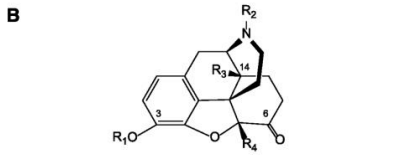
- Antagonist
  - Binds receptor and blocks effect of agonist
  - Naloxone, naltrexone

Opioids

- Endogenous
  - Beta-endorphin
  - Enkephalins
  - Dynorphins
- Natural
  - Codeine, morphine
- Semi-synthetic
  - Oxycodone, hydrocodone
  - Buprenorphine
- Synthetic
  - Fentanyl, tramadol
  - Methadone

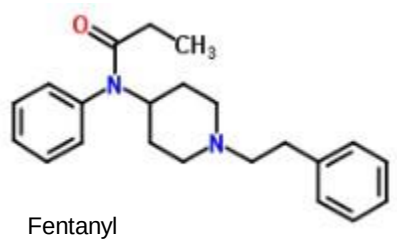


Drug	R_1	R_2	R_3	7-8 bond
Morphine	H	CH_3	H	Double
Dihydromorphine	H	CH_3	H	Single
Codeine	CH_3	CH_3	H	Double
Morphine-6-sulfate	H	CH_3	$-SO_3$	Double
Morphine-6β-glucuronide	H	CH_3	Glucuronide	Double
Heroin	Acetyl	CH_3	Acetyl	Double
6-Acetylmorphine	H	CH_3	H	Double
Nalorphine	H	Allyl	H	Double
N-Allylnorcodeine	CH_3	Allyl	H	Double



Drug	R_1	R_2	R_3	R_4
Oxymorphone	H	CH_3	OH	H
Hydromorphone	H	CH_3	H	H
Oxycodone	CH_3	CH_3	OH	H
Hydrocodone	CH_3	CH_3	H	H
Metopon	H	CH_3	H	CH_3
Naloxone	H	Allyl	OH	H
Naltrexone	H	CH_2-c-Propyl	OH	H

Gavril W. Pasternak, and Ying-Xian Pan Pharmacol Rev 2013;65:1257-1317

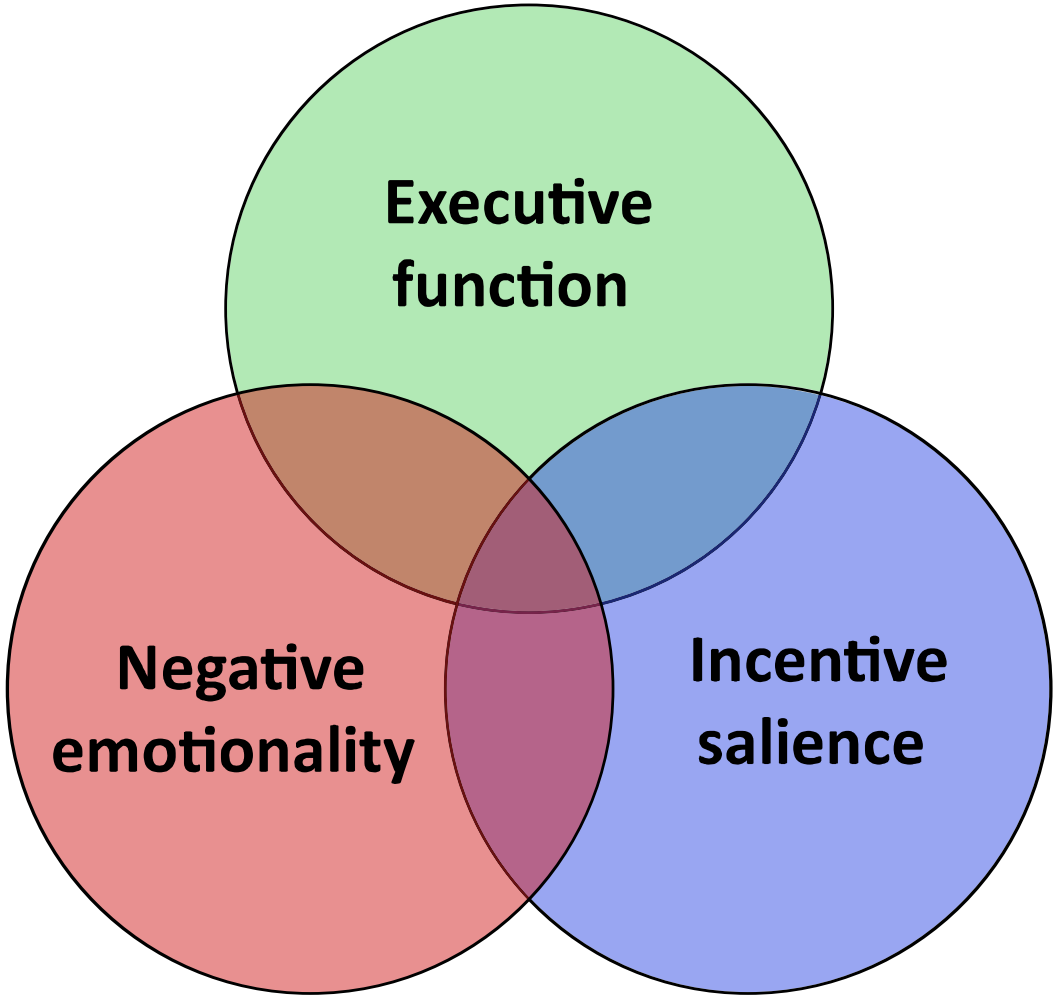


Fentanyl

Opioid receptors

- G-protein coupled 7-transmembrane receptors
  - Secondary messenger system produces effect
  - Differences in secondary messengers may produce differences in effects
- **Mu**: primary effect of analgesia, euphoria/reward, stress, respiratory, immune
- **Delta**: mood and some pain modulation
- **Kappa**: mood (dysphoria)
- **Nociceptin**: mood

Distinguishing factors of addiction



- Impaired control
- Social impairment
- Risky use
- Physical dependence
  - (Doesn't count when chronically prescribed)

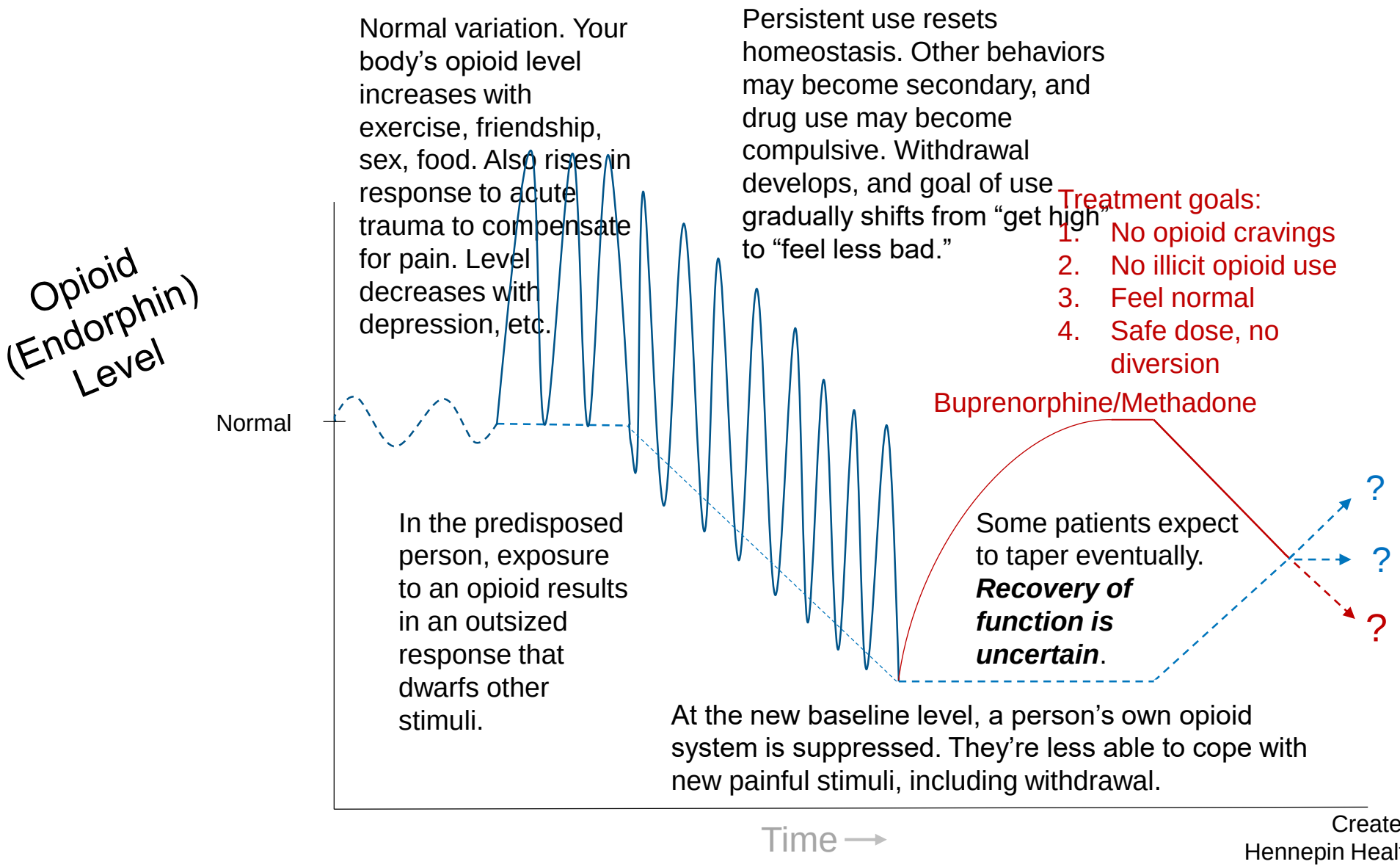
Treatment Mechanisms

- Block reinforcing effects of opioids
  - Gradual extinction of learned behaviors (conditioned responses)
- Suppress cravings for opioids
- Manage withdrawal and associated negative affect

Medications for Opioid Use Disorder

- Methadone (agonist)
- Buprenorphine (partial agonist)
  - Transmucosal (i.e., generic, Suboxone, Subutex, Zubsolv, Bunavail)
  - Implantable (Probuphine)
  - Subcutaneous depot injectable (Sublocade)
- Naltrexone (antagonist)
  - Oral (ReVia)
  - Intramuscular depot injectable (Vivitrol)

Impact of chronic opioid use and opioid maintenance therapy

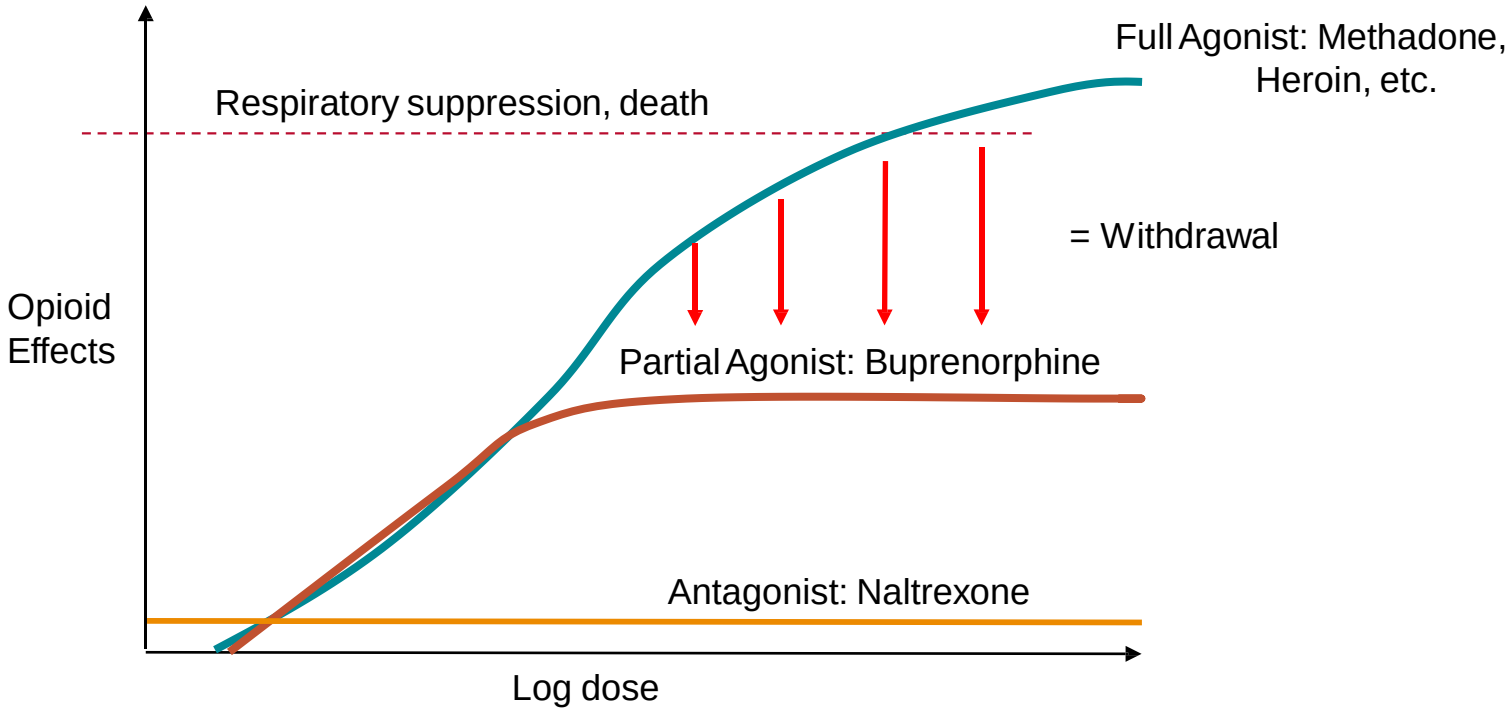


Studies suggest ***>85% of people with opioid addiction relapse without agonist medication***. A few people do well; unfortunately, we poorly predict who, how, or when to taper successfully.

Planned tapers should include close support, and recommendation to continue buprenorphine if destabilizing symptoms arise.

Created by Brian Grahan, MD, PhD on 4/1/18
Hennepin Healthcare Opioid & Addictions Care ECHO

Clinical pharmacology of MOUD



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Methadone

8/22/2019

Pharmacology for Opioid Use Disorder: **Methadone**

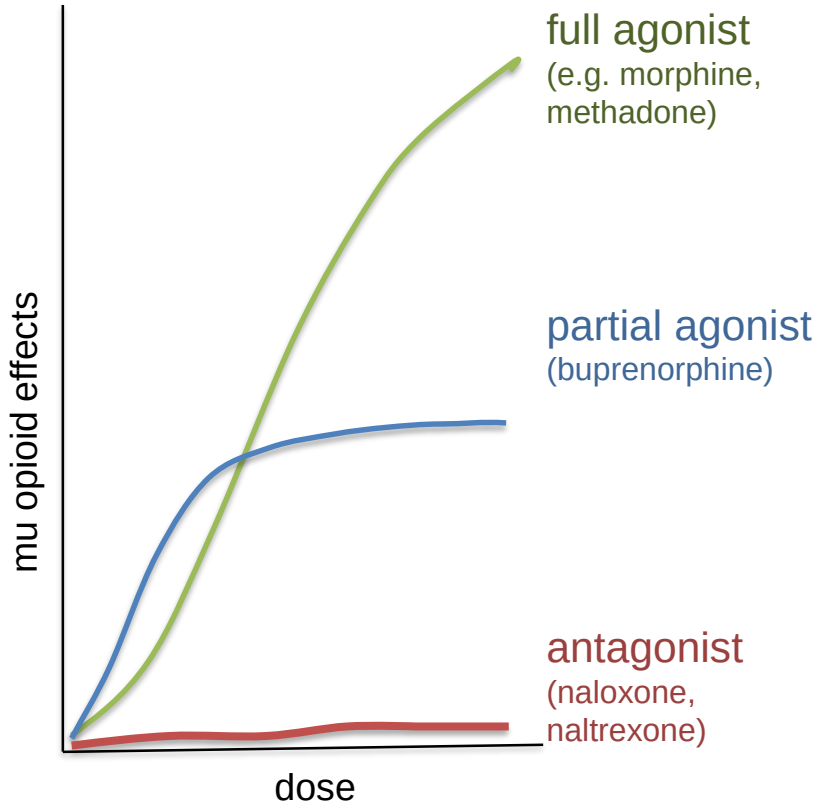
***Full Agonist* at mu receptor**

Long acting

- Half-life ~ 15-60 Hours

Monitoring

- Significant respiratory suppression and potential respiratory arrest in overdose
- Does not impair driving at stable doses



CSAT, 2005

Pharmacotherapy for Opioid Use Disorder: **Methadone**

- Effective dose:
  - Dose 20-40 mg for acute withdrawal (suppression by 60 mg)
  - 80-120 mg for craving and “blockade” (although weak mu receptor affinity)
- Analgesia mean duration 5-8 hours
  - NMDA antagonist
- Many drug-drug interactions given complicated hepatic metabolism
- May prolong QTc

<u>Monitoring</u>

- To evaluate stability, ask about take-home doses
- Only R-methadone enantiomer has opioid activity, so total levels uninterpretable
- **Multiple** medication interactions due to multi-faceted CYP450 metabolism

Clinical use: **Methadone**

- Most effective
  - ↑ survival, treatment retention, employment
  - ↓ illicit opioid use, hepatitis and HIV infections, criminal activity
- Highly regulated, dispensed at Opioid Treatment Programs (OTP)
  - Supervised daily liquid administration with take-home doses if stable in treatment
  - Counseling, urine testing
  - Psychiatric, medical services often not provided
  - **Illegal** to prescribe methadone **for addiction** in general practice
- Excellent outcomes for pregnant women with OUD
- May prescribe for 3 days of directly observed therapy while arranging entry into OTP
- May prescribe indefinitely to hospitalized patient
  - Already on methadone, or
  - With an untreated OUD hospitalized for any reason other than OUD as primary dx

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Buprenorphine

8/22/2019

Pharmacotherapy for Opioid Use Disorder: **Buprenorphine**

Partial agonist at mu receptor

- Minimal respiratory suppression and no respiratory arrest when used as prescribed

Long acting

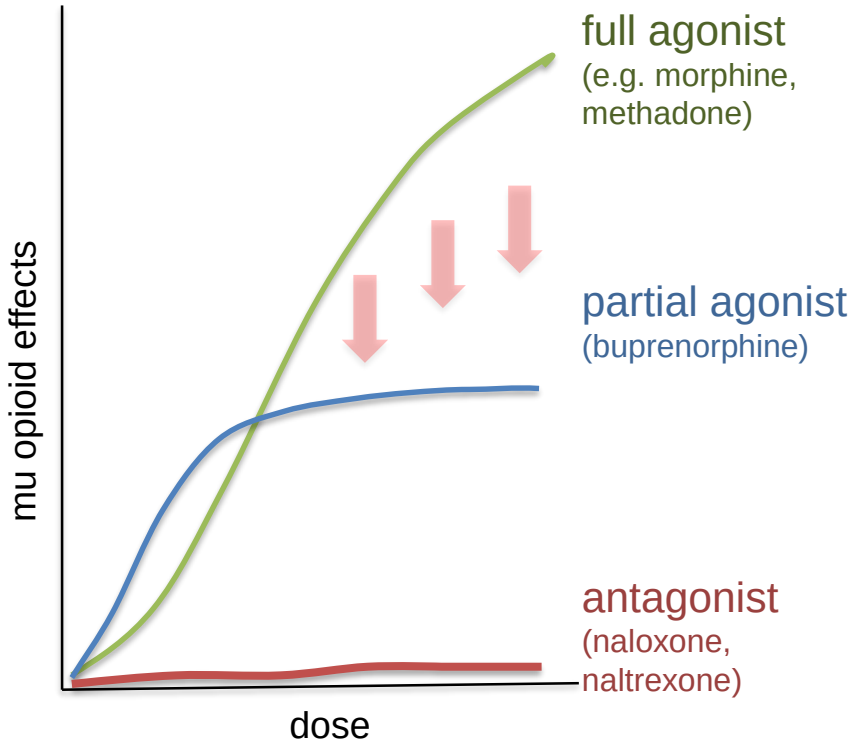
- Half-life ~ 24-36 Hours

High affinity for mu receptor

- *Blocks* other opioids
- *Displaces* other opioids (can precipitate withdrawal)

Slow dissociation from mu receptor

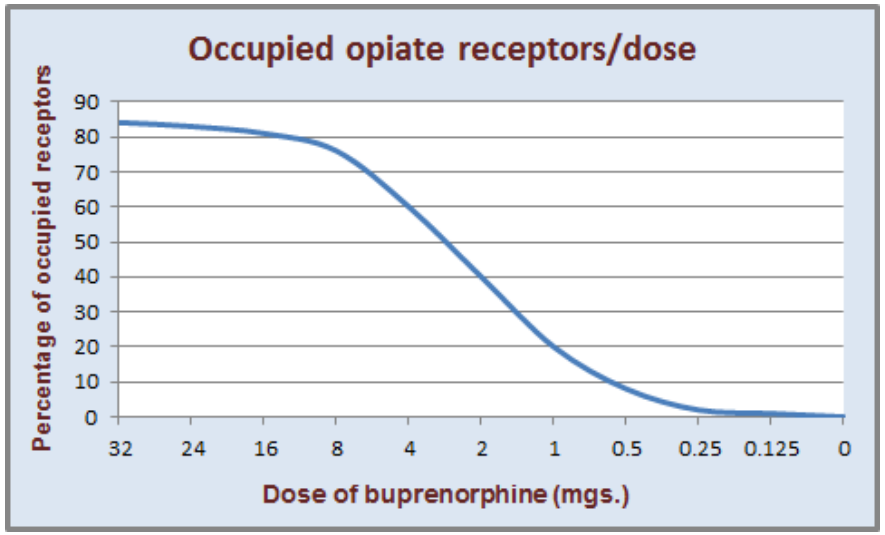
- *Stays on receptor for a long time*



SAMHSA, 2018
Orman & Keating, 2009

Pharmacotherapy for Opioid Use Disorder: **Buprenorphine**

- Primary metabolism by CYP3A4
  - Extensive 1st pass metabolism (poor oral bioavailability)
  - Few drug-drug interactions
- Biliary tract >> urinary excretion
  - Buprenorphine and norbuprenorphine detectable in urine
- Target dose ~ 16mg daily, max dose 24mg *for OUD*
  - Higher dose may have greater analgesic effect

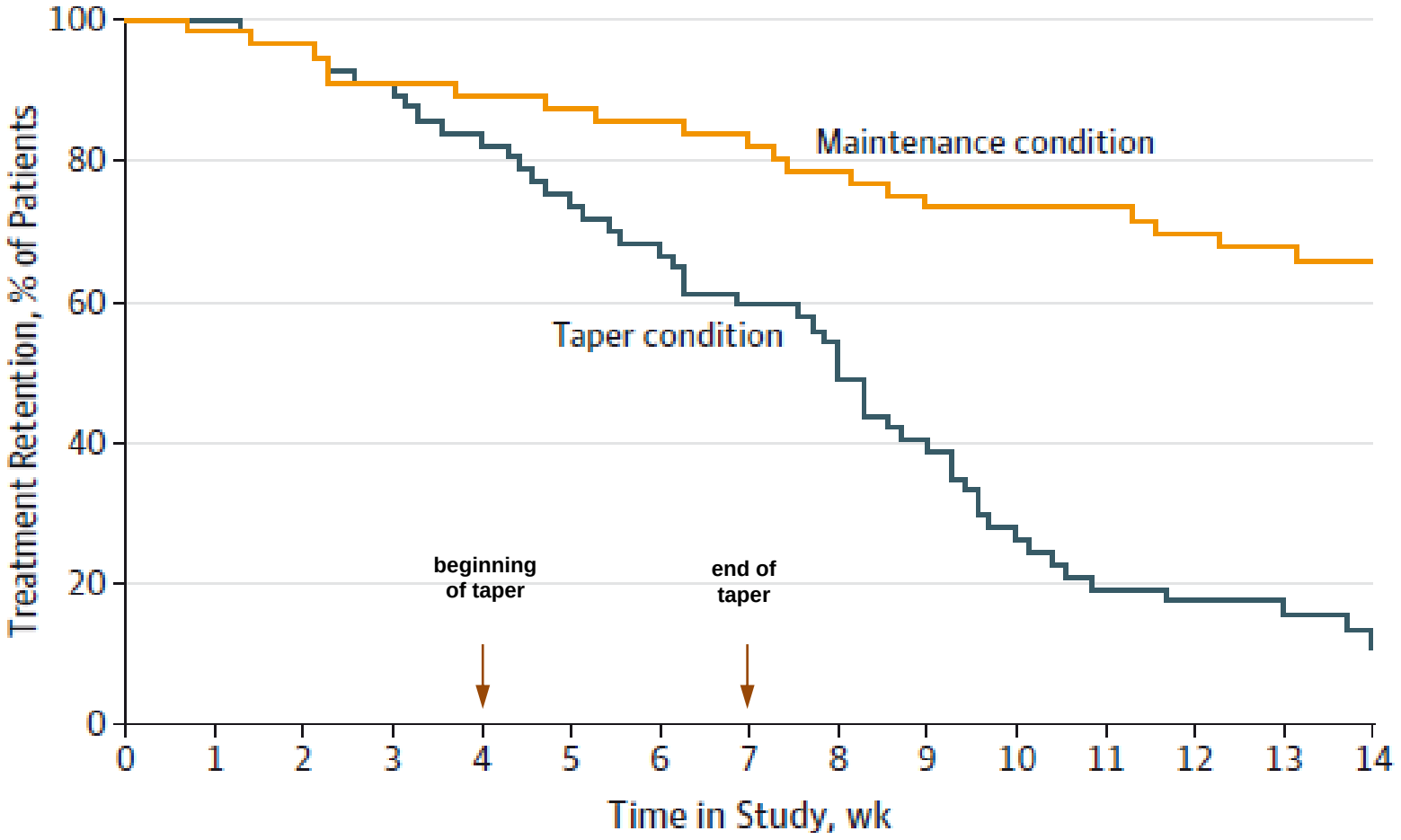


Mendelson et al., 1997
SAMHSA, 2016,; SAMHSA, 2018

Clinical use: **Buprenorphine**

- 2000 Federal Drug Addiction Treatment Act ("DATA-2000"):
  - Legalized office-based addiction treatment by physicians
  - Required 8-hr training and federal waiver for physicians, 24-hr for APPs
- 2002: Suboxone (buprenorphine/naloxone) FDA approved
  - Schedule III
  - Outcomes much superior to psychosocial treatment alone
  - Longer treatment duration more effective
- Compared to methadone:
  - Similar abstinence from illicit opioids and decreased craving
  - Slightly lower retention in treatment
  - Can be prescribed in general practice

Sublingual Buprenorphine: Maintenance vs. Taper



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Fiellin et al., 2014

Subcutaneous injectable depot buprenorphine

- FDA approved formulation = Sublocade (*Indivior*)
  - 4 week depot SC injection
  - Recommended dose 300 mg injection x2, then 100 mg injections
  - Comparable adverse effects + injection site pruritis (6%)
  - Administered after ≥7 day stabilization on SL buprenorphine 8-24 mg
  - No comparison trials with sublingual or buccal buprenorphine

Common adverse effects of buprenorphine

- Headaches
  - Management: aspirin, ibuprofen, acetaminophen (if there are no contra-indications)
- Nausea
  - Management: Consider spitting the saliva out after adequate absorption instead of swallowing
- Constipation
  - Management: Stay well-hydrated, high-fiber diet, stool softeners, laxatives, naloxegol
- Xerostomia (Dry mouth) – side effect of ALL opioids
  - Complications: Gingivitis, Periodontitis
  - Management: Stay well-hydrated, Maintain good oral hygiene

SAMHSA, 2018
Wald, 2016

Buprenorphine and benzodiazepines

- Benzodiazepines present in most fatal poisonings involving buprenorphine

Human studies	Minimal effects on respiration when both are taken at therapeutic doses
Animal studies	May remove the protective "ceiling effect" and allow buprenorphine to produce fatal respiratory suppression in overdose

- **Used-as-prescribed benzodiazepines** in combination with buprenorphine have only been associated with more accidental injuries, not with mortality and other safety or treatment outcomes

Bardy et al., 2015; Jones et al., 2012
Nielsen & Taylor, 2005; Schuman-Olivier et al., 2013

Changes in FDA Recommendations

08/2016	09/2017
▪ Boxed Warning for combined use of opioid medicines with benzodiazepines or other CNS Depressants (e.g. Alcohol) ▪ Risks of slowed or difficult breathing; Sedation; Death	▪ Buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). ▪ The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks. ▪ Careful medication management by health care professionals can reduce these risks.

FDA, 2016, 2017

Rationale for combining buprenorphine with naloxone

- When used as prescribed (sublingual or buccal administration), there is minimal bioavailability of naloxone
- Compared to bup alone, the bup/nlx combination:
  - is more likely to precipitate withdrawal if injected by a current opioid user
  - produces a slowed onset effect when injected or insufflated in those who are physically dependent on buprenorphine
  - per prescription, is less likely to be diverted

Mendelsohn, 1997; Comer et al., 2010
Jones et al., 2015; Stoller et al., 2001

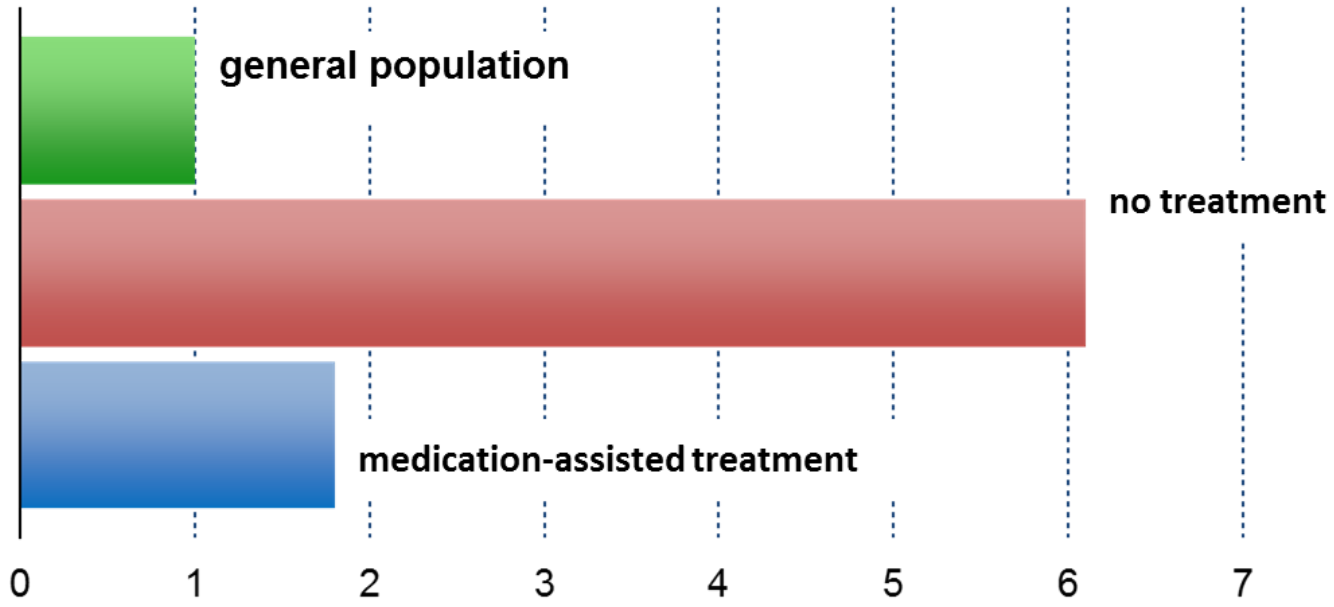
Buprenorphine diversion

- Has intravenous misuse potential but <1% report bup use for intoxication
- Variable market preference for tablets vs films
- Mono-product (Subutex) tablets probably preferred on street to bup/nlx
- In a survey of more than 4,000 patients in treatment programs in the United States, relative rates of diversion per prescribed dose were:
  - **buprenorphine/naloxone film: 1** (reference)
  - **buprenorphine/naloxone tablet: 2.2**
  - **buprenorphine tablet: 6.5**
- Therefore, buprenorphine/naloxone is standard of care

Comer et al., 2010; Jones et al., 2015
Larancea et al., 2014; Lavonas et al., 2014

Benefits of ***agonist*** MOUD: Decreased Mortality

Death rates:



Dupouy et al., 2017
Evans et al., 2015
Sordo et al., 2017

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Naltrexone

8/22/2019

Pharmacotherapy for Opioid Addiction: **Naltrexone**

Full Antagonist at mu receptor

- Competitive binding

Long acting

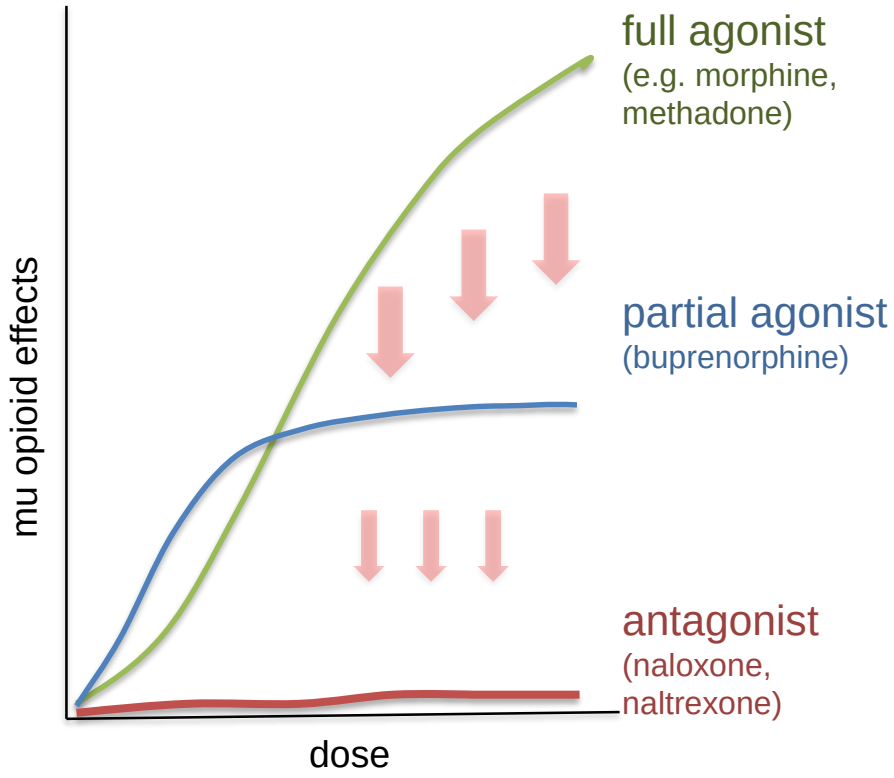
- Active 1st metabolite (6-beta-naltrexol)
- IM $t_{1/2}$ ~ 5-10 days

High affinity for mu receptor

- *Blocks & displaces* other opioids

Formulations

- Tablets not used due to poor adherence
- Extended-Release IM injection: *Vivitrol*®



SAMHSA, 2018

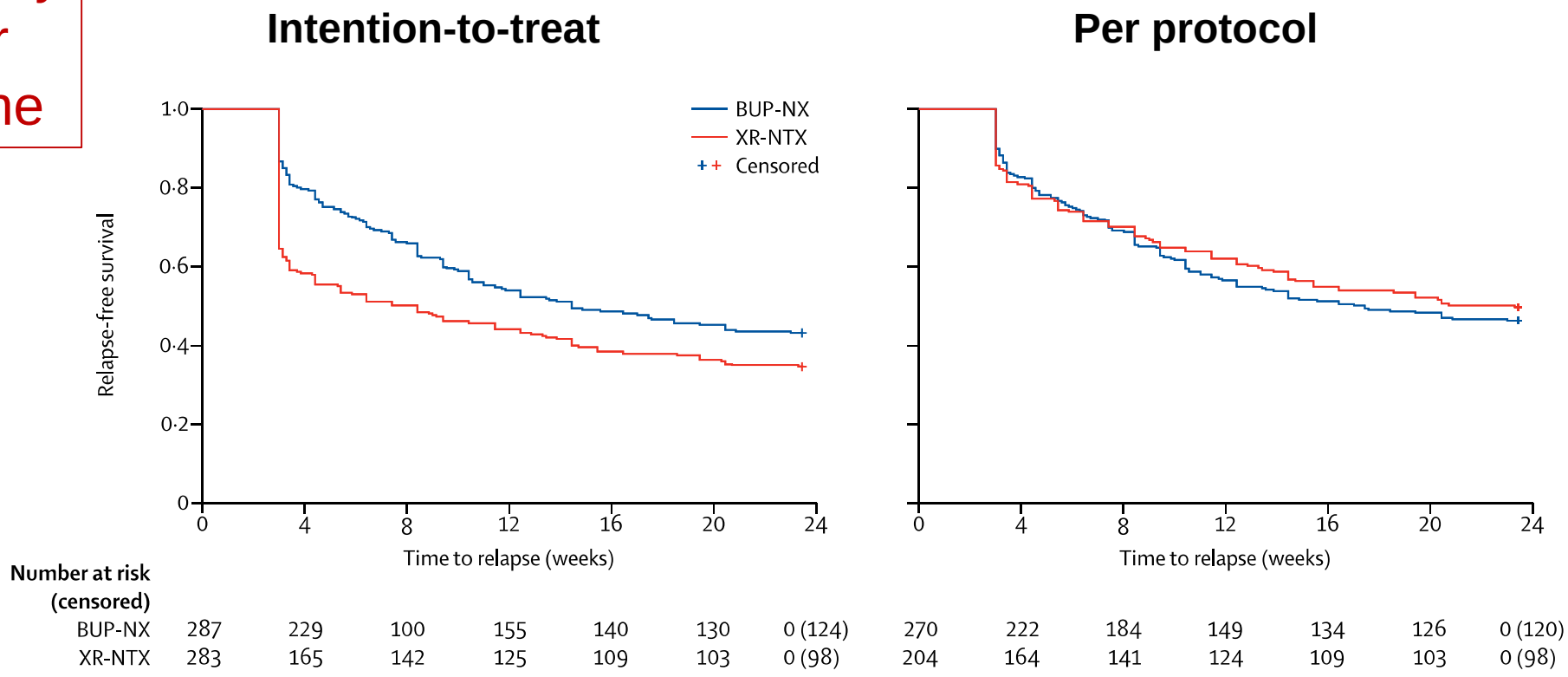
Intramuscular depot naltrexone for opioid use disorder

- Requires 3-7 days of opioid abstinence prior to initiation with pre-injection naloxone challenge or negative urine drug test

- In comparative RCT of bup/nlx vs IM depot naltrexone (XR-NTX) in patients *at detox* (Lee JD at al, 2017):
  - XR-NTX 28% drop out before induction versus only 6% for Suboxone
  - Cravings only suppressed in ~60% of patients
  - Nearly all induction failures had early relapse
  - Once inducted, XR-NTX and BUP-NX similar effect for 6 months
  - Overdose and other serious adverse event rates did not differ

Sublingual buprenorphine (BUP-NX) vs IM depot naltrexone (XR-NTX)

No mortality data for naltrexone



Lee JD et al. Lancet. 2017

MOUD in Pregnancy

- Agonist therapy is standard of care in pregnancy
  - No risk of birth defects
  - Opioid risks or miscarriage and premature labor associated with withdrawal in early 1st trimester and late 3rd trimesters

- Risk of neonatal opioid withdrawal syndrome
  - Not associated with long-term cognitive, developmental, or other sequelae

- Stable mother and family best predictor of infant success

- No reasonable evidence related to naltrexone on pregnancy and fetal outcomes

Overdose Prevention

- Naloxone (“Narcan”) reverses opioid overdose
- Overdose education and naloxone is an effective harm reduction strategy
- For those at high risk of overdose and their friends or family
  - Steve’s Law in MN allows third party prescribing
  - Easy to protocol for pharmacy distribution
- Populations: syringe exchange, release from incarceration, in drug treatment, high risk prescribed opioids
- Prescribe to Prevent educational modules: http://www.opioidprescribing.com/naloxone_module_1-landing

Notes on overdose

- Fentanyl and analogues are very potent
  - Increased chance of adverse effects esp. if low tolerance

- Very high potency ≠ affinities are too high for:
  - Naloxone to reverse overdose
  - MOUD to be effective

- Related but not equal to MME

Notes on opioid analgesia

- Methadone and buprenorphine provide opioid-responsive analgesia for 4-6 hours/dose

- Other opioid analgesics may still work in setting of agonist therapy
  - Higher doses (1.5-2x) of usual full opioid agonist often required
    - Usual duration and frequency of therapy
  - Higher affinity opioids often needed with buprenorphine
    - May need to reduce buprenorphine dose <16 mg daily

- Opioid analgesia *very* difficult while on naltrexone
  - Possible with high dose IV fentanyl drip in ICU

Caveat emptor:
Morphine Milligram Equivalents (MME)

- Not based on pharmacology *per se*
- Based on pain relief response
- Doesn't apply to MOUD
- Acute versus chronic therapy
- Not meant for dose conversions
- Helpful for pharmacoepidemiology

Checklist for prescribing opioids for chronic pain

For primary care providers treating adults (18+) with chronic pain ≥3 months, excluding cancer, palliative, and end-of-life care

CHECKLIST

When CONSIDERING long-term opioid therapy

- ☐ Set realistic goals for pain and function based on diagnosis (eg, walk around the block).
- ☐ Check that non-opioid therapies tried and optimized.
- ☐ Discuss benefits and risks (eg, addiction, overdose) with patient.
- ☐ Evaluate risk of harm or misuse.
  - Discuss risk factors with patient.
  - Check prescription drug monitoring program (PDMP) data.
  - Check urine drug screen.
- ☐ Set criteria for stopping or continuing opioids.
- ☐ Assess baseline pain and function (eg, PEG scale).
- ☐ Schedule initial reassessment within 1–4 weeks.
- ☐ Prescribe short-acting opioids using lowest dosage on product labeling; match duration to scheduled reassessment.

If RENEWING without patient visit

- ☐ Check that return visit is scheduled ≤3 months from last visit.

When REASSESSING at return visit

Continue opioids only after confirming clinically meaningful improvements in pain and function without significant risks or harm.

- ☐ Assess pain and function (eg, PEG); compare results to baseline.
- ☐ Evaluate risk of harm or misuse:
  - Observe patient for signs of over-sedation or overdose risk.
    - If yes: Taper dose.
  - Check PDMP.
  - Check for opioid use disorder if indicated (eg, difficulty controlling use).
    - If yes: Refer for treatment.
- ☐ Check that non-opioid therapies optimized.
- ☐ Determine whether to continue, adjust, taper, or stop opioids.
- ☐ Calculate opioid dosage morphine milligram equivalent (MME).
  - If ≥50 MME/day total (≥50 mg hydrocodone; ≥33 mg oxycodone), increase frequency of follow-up; consider offering naloxone.
  - Avoid ≥90 MME/day total (≥90 mg hydrocodone; ≥60 mg oxycodone), or carefully justify; consider specialist referral.
- ☐ Schedule reassessment at regular intervals (≤3 months).

REFERENCE

EVIDENCE ABOUT OPIOID THERAPY

- *Benefits of long-term opioid therapy for chronic pain not well supported by evidence.*
- *Short-term benefits small to moderate for pain; inconsistent for function.*
- *Insufficient evidence for long-term benefits in low back pain, headache, and fibromyalgia.*

NON-OPIOID THERAPIES

Use alone or combined with opioids, as indicated:

- Non-opioid medications (eg, NSAIDs, TCAs, SNRIs, anti-convulsants).
- Physical treatments (eg, exercise therapy, weight loss).
- Behavioral treatment (eg, CBT).
- Procedures (eg, intra-articular corticosteroids).

EVALUATING RISK OF HARM OR MISUSE

Known risk factors include:

- Illegal drug use; prescription drug use for nonmedical reasons.
- History of substance use disorder or overdose.
- Mental health conditions (eg, depression, anxiety).
- Sleep-disordered breathing.
- Concurrent benzodiazepine use.

Urine drug testing: Check to confirm presence of prescribed substances and for undisclosed prescription drug or illicit substance use.

Prescription drug monitoring program (PDMP): Check for opioids or benzodiazepines from other sources.

ASSESSING PAIN & FUNCTION USING PEG SCALE

PEG score = average 3 individual question scores (30% improvement from baseline is clinically meaningful)

Q1: *What number from 0–10 best describes your pain in the past week?*
0="no pain", 10="worst you can imagine"

Q2: *What number from 0–10 describes how, during the past week, pain has interfered with your enjoyment of life?*
0="not at all", 10="complete interference"

Q3: *What number from 0–10 describes how, during the past week, pain has interfered with your general activity?*
0="not at all", 10="complete interference"

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

TO LEARN MORE
WWW.CDC.GOV/DRUGOVERDOSE/PRESCRIBING/GUIDELINE

March 2016

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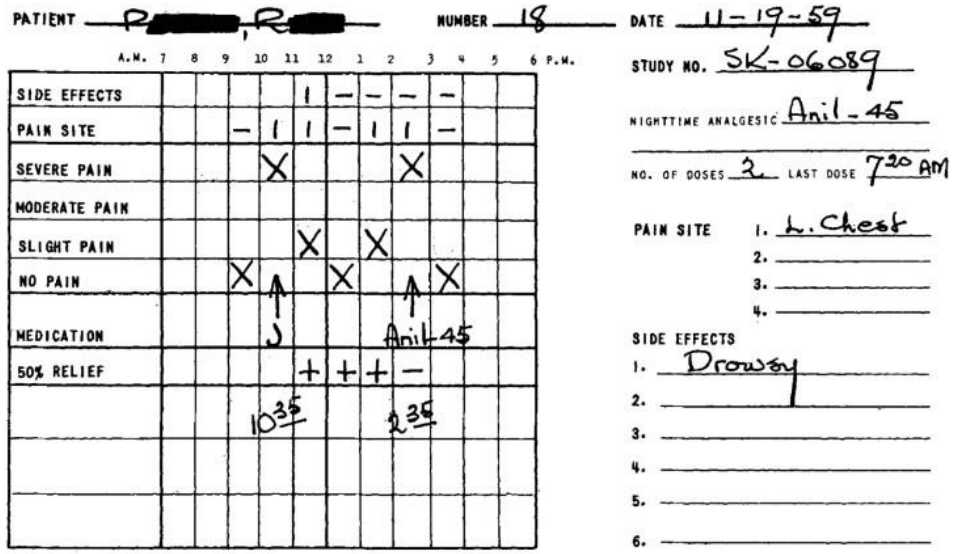
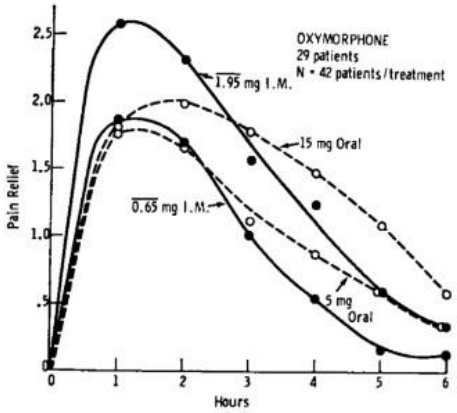
Morphine Milligram Equivalents (MME)





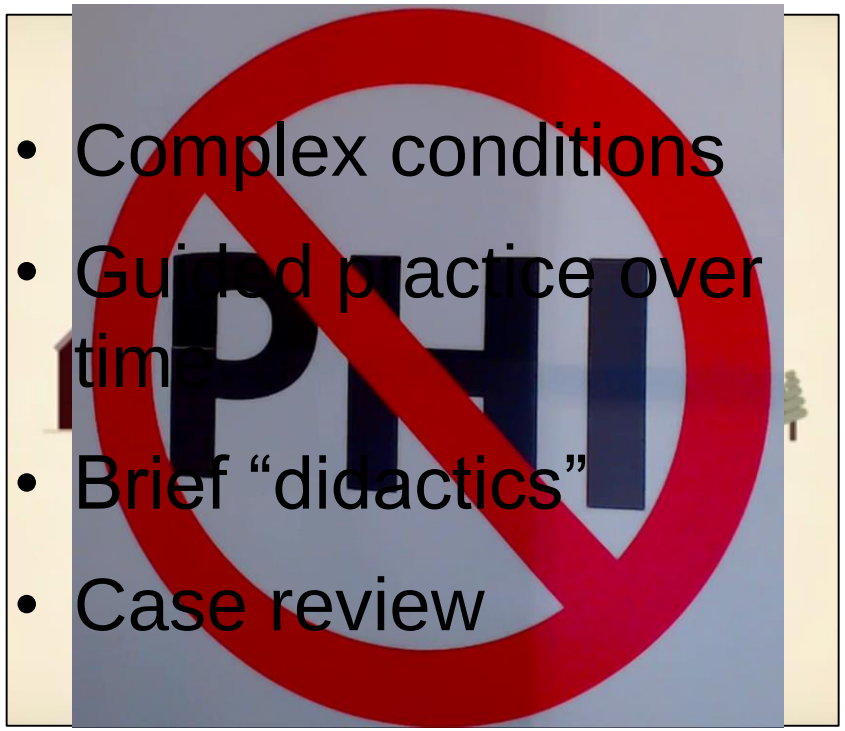
Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors[1,2]

Type of Opioid (strength units)	MME Conversion Factor
Buprenorphine film/tablet[3] (mg)	30
Buprenorphine patch[4] (mcg/hr)	12.6
Buprenorphine film (mcg)	0.03
Butorphanol (mg)	7
Codeine (mg)	0.15
Dihydrocodeine (mg)	0.25
Fentanyl buccal or SL tablets, or lozenge/troche[5] (mcg)	0.13
Fentanyl film or oral spray[6] (mcg)	0.18
Fentanyl nasal spray[7] (mcg)	0.16
Fentanyl patch[8] (mcg)	7.2
Hydrocodone (mg)	1
Hydromorphone (mg)	4
Levorphanol tartrate (mg)	11
Meperidine hydrochloride (mg)	0.1
Methadone[9] (mg)	3
>0, <= 20	4
>20, <=40	8
>40, <=60	10
>60	12
Morphine (mg)	1
Opium (mg)	1
Oxycodone (mg)	1.5
Oxymorphone (mg)	3
Pentazocine (mg)	0.37
Tapentadol [10] (mg)	0.4
Tramadol (mg)	0.1

Integrated Opioid & Addiction Care

- Fun, case-based, interactive tele-mentoring via videoconference
- Network of mentors & colleagues
- Thursdays 12:15 – 1:15
- Free AMA PRA Category 1 Credit™ per session

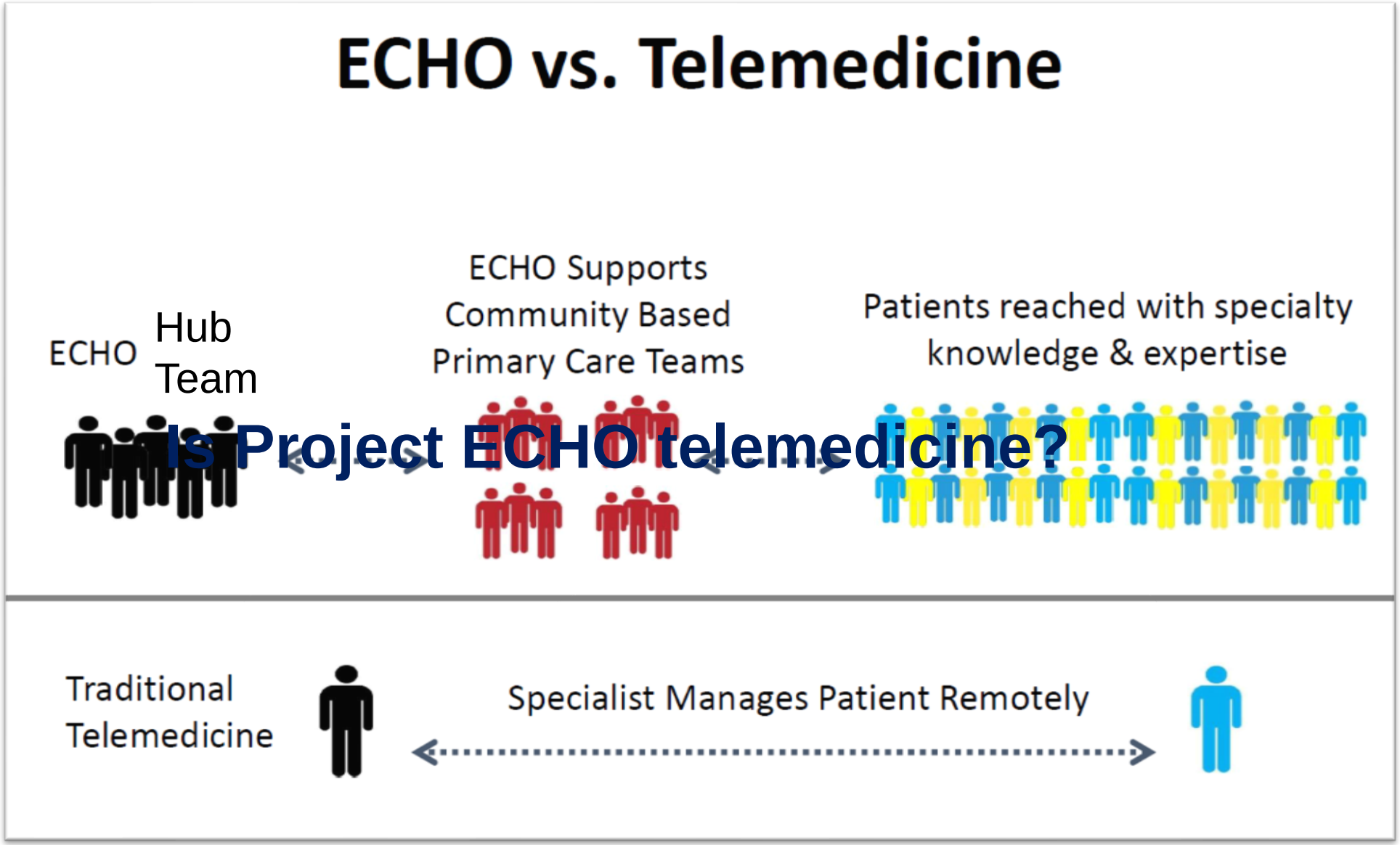
How does Project ECHO work?



- Complex conditions
- Guided practice over time
- Brief “didactics”
- Case review

“Moving knowledge, not patients”

ECHO vs. Telemedicine



Is Project ECHO telemedicine?

Source: Michelle Iandiorio, MD, Project ECHO New Mexico

Medications for Opioid Use Disorder Summary

	Methadone	Buprenorphine (Oral)	Naltrexone (IM)
Mechanism of Action	Full Agonist on Opioid Receptor	Partial Agonist on Opioid Receptor	Antagonist on Opioid Receptor
Dosing	80mg-100mg (Usual Dose)	4-32mg	380mg Depot Injection
Advantages	▪ Provided in a highly structured supervised setting where additional services can be provided on-site and diversion is unlikely ▪ Maybe effective for individuals who have not benefited sufficiently from partial agonists or antagonists	▪ Improved safety due to partial agonism ▪ Availability in office-based settings	▪ No addictive potential or diversion risk ▪ Available in office-based settings ▪ Option for individuals seeking to avoid any opioids

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Questions?