Buprenorphine Prescribing

Prescribing and Review of Evidence

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Disclosures

None

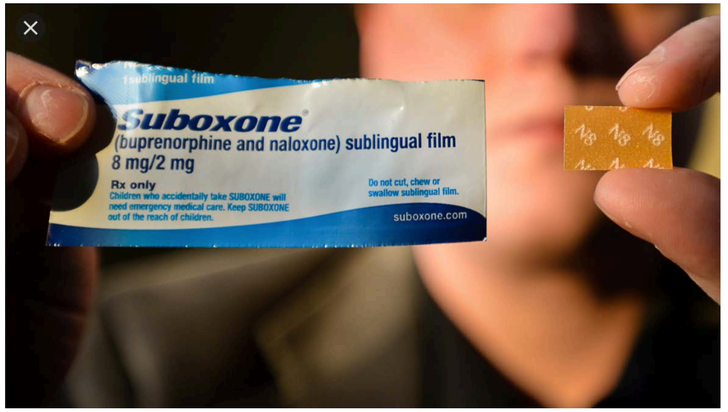
Learning Objectives

At the end of this presentation participants should be able to:

- Describe the mechanism of action of buprenorphine
- Perform induction prescribing
- Apply data informing current prescribing best practices
- Discuss data supporting buprenorphine for chronic pain

Medications for Opiate Use Disorder Are Effective

methadone or buprenorphine treatment reduced relapse risk by approximately 50% compared to behavioral treatment alone



Clark R, et al. Risk Factors for Relapse and Higher Costs Among Medicaid Members with Opioid Dependence or Abuse: Opioid Agonists, Comorbidities, and Treatment His History. *Journal of Substance Abuse Treatment.* 2015; 57:75-80.

Forms of Buprenorphine

Administration	Generic	Brand	FDA approvals
Sublingual Film or Sublingual Tablet	Buprenorphine + Naloxone	*Suboxone, Zubzolv*	Opioid Use Disorder
Sublingual Tablet	Buprenorphine	*Subutex*	Opioid Use Disorder Pain
Subcutaneous Injection Q4 weeks	Buprenorphine	*Sublocade*	Opioid Use Disorder
Transdermal Patch	Buprenorphine	*Butrans*	Pain
Buccal Strip	Buprenorphine	*Belbuca*	Pain
6-month Implantable Rods (similar to Nexplanon)	Buprenorphine	*Probuphine*	Opioid Use Disorder

Bioavailability

Buprenorphine:

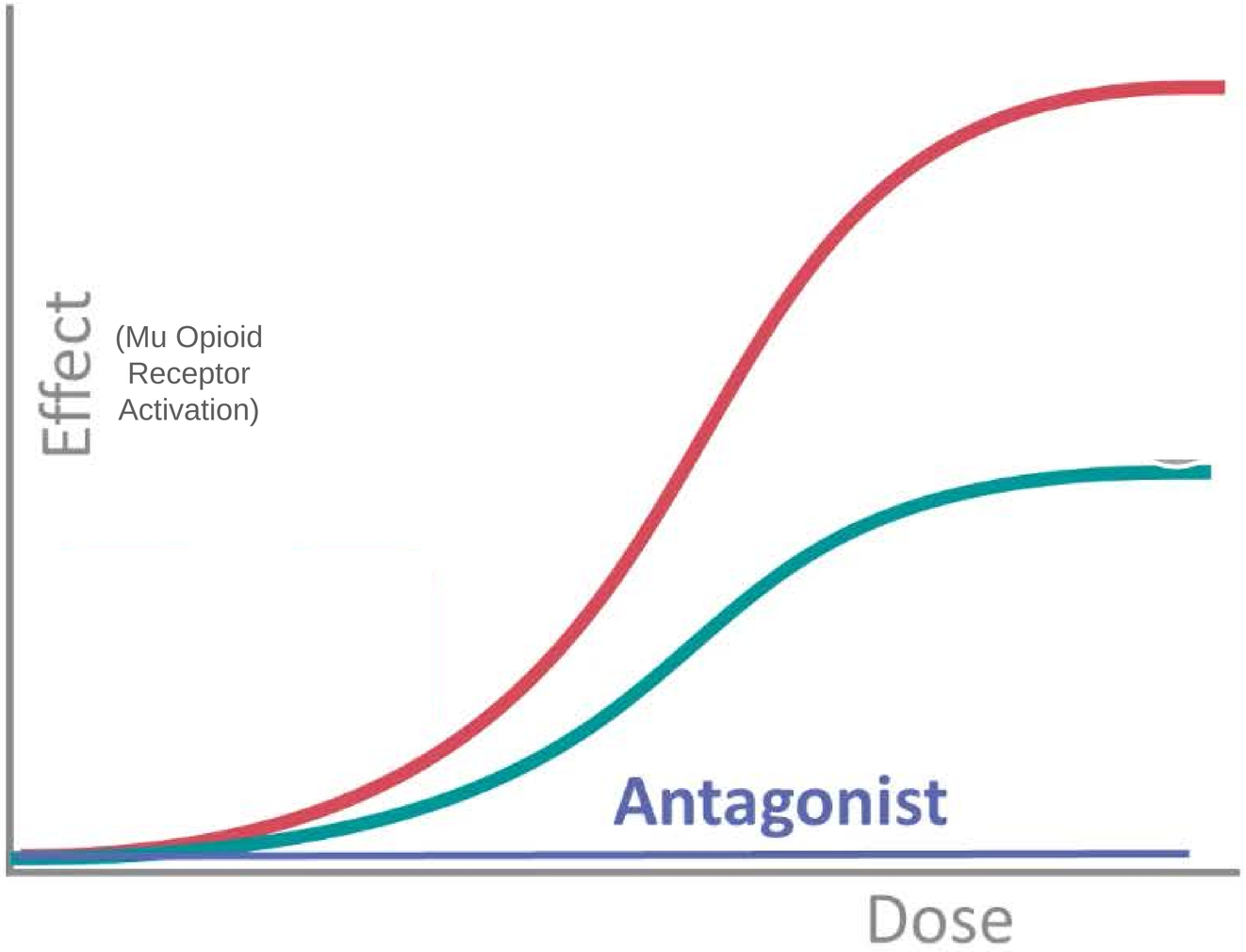
- Sublingual (left until fully dissolved): 25-40%
- PO (swallowed): 16%
- Parenteral (injected, eyelids, intranasal): more than 50%

Naloxone:

- Sublingual: < 3%
- PO: very low
- Parenteral: >30%

Coe M, et al. Buprenorphine Pharmacology Review: Update on Transmucosal and Long-acting Formulations. *Journal of Addiction Medicine,* March/April 2019;13(2): 93-103

Buprenorphine vs. Other Opioids



Full agonist: Heroin and others

Partial agonist: Buprenorphine

Ceiling effect

Safety: less respiratory depression
Less euphoric effect
Patients don’t typically advance their dose

Lufty K. & Cowan A. Buprenorphine: a unique drug with complex pharmacology. *Current Neuropharmacology,* 2004; 2(4): 395-402 / Psychopharmacology Institute

How to Start Buprenorphine (induction)

- Prescribe Buprenorphine/Naloxone 8/2mg, #28
- Instruct patient to wait until they are in moderate withdrawal (anxiety, some nausea with no vomiting, sweating, musculoskeletal aches)
- Then take initial dose: half to whole 8/2mg tab or film sublingually
- Instruct patient to add an additional half or whole tab/film every hour until relief
  The total final dose is typically the once daily maintenance dose
- Max dose for day one is 16/4mg
- Patient can increase to 24/6mg the second day if needed
- Be sure to prescribe Naloxone (Narcan)
  It’s the law in New Mexico

Which works better: Home or Office Induction?

- 20 patients randomized to unobserved (home induction) vs. office-based
- Both groups instructed to take no more than 16mg on first day
- Outcome results were similar in the two groups:

  60% successfully induced in both groups

  30% experienced prolonged withdrawal in both groups

  40% stabilized by week 4 in both groups

Gunderson EW et al. Unobserved Versus Observed Office Buprenorphine/Naloxone Induction: a pilot randomized clinical trial. *Addict Behav.* May 2010;35(5):537-40

Why Prescribe at Least a 2-Week Supply?

- Fewer initial days of supply were associated with increased odds of discontinuation (OR=1.32, P<0.01)

- Fewer initial days of supply associated with INCREASED adverse events (eme

Meinhofer A, et al. Prescribing decisions at buprenorphine treatment initiation: Do they matter for treatment discontinuation and adverse opioid-related events? *J Subst Abuse Treat.* October 2019;105:37-43

Why Prescribe at Least 16/2mg initial dose?

- Patients prescribed medium dose (16/4mg) or high dose (24/6mg) buprenorphine prescriptions had higher odds of 180-day adherence than those filling low dose prescriptions (8/2mg)

- For 16mg initial dose: OR = 1.76
- For 24mg initial dose: OR = 5.11

Pizzicato L, et al. Adherence to Buprenorphine: An analysis of prescription drug monitoring program data. *Drug Alcohol Depend*. Nov 2020

Buprenorphine Taper vs Maintenance?

Should we detox using Buprenorphine, and then taper?

- 14 week randomized trial, 113 patients with Prescription Opioid Dependence
- **Taper group:** stabilized for 6 weeks - then tapered over 3 weeks - medications for withdrawal were offered during taper - naloxone treatment offered after taper
- **Maintenance Group:** stabilized then offered ongoing Buprenorphine for total of 14 weeks

	Mean % of opioid free urine samples	Mean reported consecutive weeks of opioid abstinence	Likelihood to complete the trial
Taper Group	35.2%	2.70 weeks	11%
Maintenance Group	53.2%	5.20 weeks	66%

Fiellin D, et al. Primary Care-Based Buprenorphine Taper vs Maintenance Therapy for Prescription Opioid Dependence, A Randomized Clinical Trial
JAMA Internal Medicine 2014;174(12):1947-1954

Should Buprenorphine be Prescribed to Patients on a Benzodiazepine?

In 2016 the CDC recommended:

“Avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible” (CDC’s Guideline for Prescribing Opioids for Chronic Pain, 2016)

In 2017 the FDA advised:

“Opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines…careful medication management can reduce risks” (FDA Safety Announcement: 9-20-2017)

Buprenorphine + Benzo/Z-drug Overdose Risk

Does overdose risk increase with the combination?

- 23,000 persons age 12-64
- 14,000,000 person-days of observation time
- Exposures were Buprenorphine prescriptions, Benzodiazepine prescriptions and Z-Drug prescriptions.
- Outcome of interest was any nonfatal drug-related poisonings

Xu K, et al. Association Between Benzodiazepine or Z-Drug Prescriptions and Drug-Related Poisonings Among Patients Receiving Buprenorphine Maintenance: A case-crossover analysis. *American Journal of Psychiatry* 2021;178(7):651-659.

Buprenorphine + Benzo/Z-drug Overdose Risk

Does overdose risk increase with the combination?

- Buprenorphine treatment vs non-treatment days
  40% reduction in poisoning events (OR=0.63)

- Benzodiazepine or Z-drug treatment days
  88% increase in poisoning events

Low dose defined as:
< 3mg of Alprazolam
< 6mg of Lorazepam
< 3mg of Clonazepam
< 30mg of Diazepam

- Low-dose benzodiazepine treatment + buprenorphine: **no increased poisonings**

- High-dose benzodiazepine treatment + buprenorphine: **increased poisoning risk (OR=1.64)**

- Poisoning Odds Ratios for benzodiazepine or Z-drug treatment without buprenorphine:
  low dose Bzd/Z-drug: **OR=1.69**
  high dose Bzd/Z-drug: **OR=2.23**

Xu K, et al. Association Between Benzodiazepine or Z-Drug Prescriptions and Drug-Related Poisonings Among Patients Receiving Buprenorphine Maintenance: A case-crossover analysis. *American Journal of Psychiatry* 2021;178(7):651-659.

What's the Evidence for Higher Buprenorphine Doses?

Is it worth going above 24mg per day?

- 1267 patients
- in 9 treatment programs
- randomized to receive open label Buprenorphine or Methadone
- for 24 weeks
- Endpoint: treatment retention

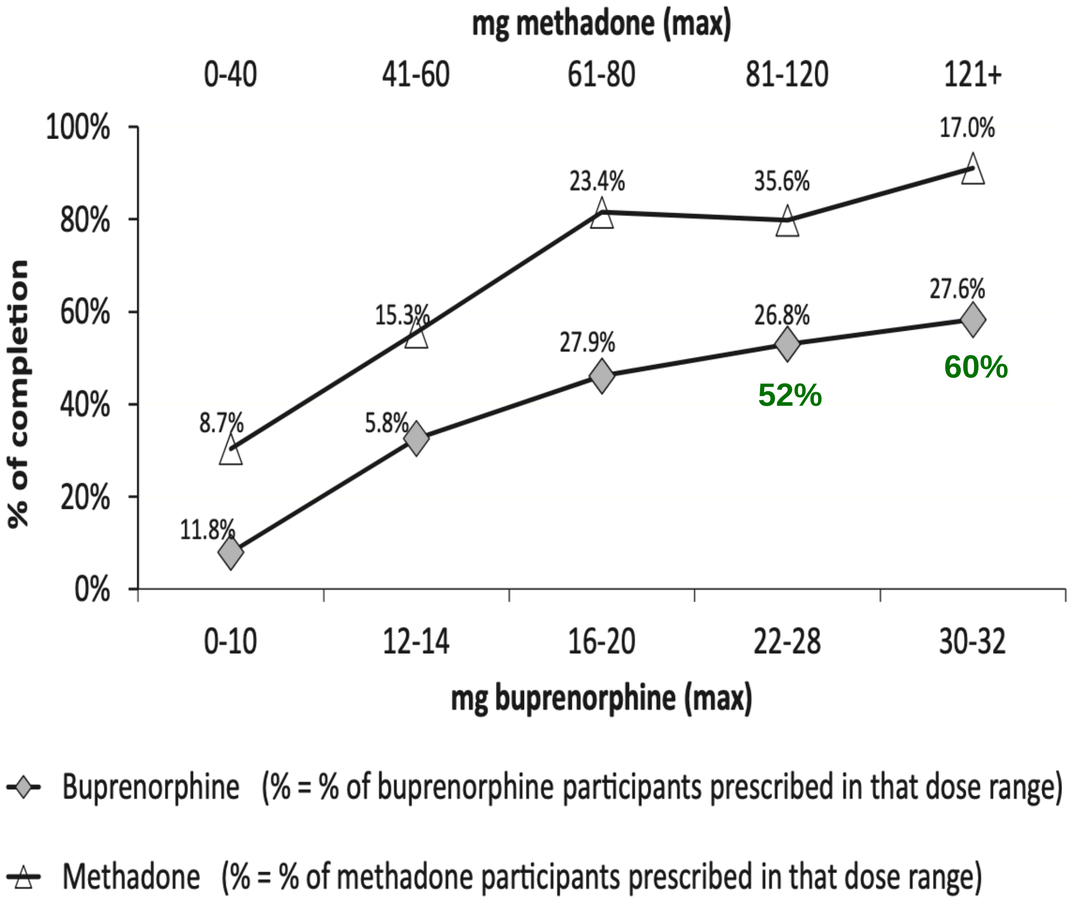


Figure 2 Comparing retention at 24 weeks by maximum dose of medication prescribed

Hser Y, et al. Treatment retention among patients randomized to bup/naloxone compared to methadone in a multi-site trial. *Addiction* 2013;109:19-87

Prescribing Pearls

- The dose required to address CRAVINGS is usually higher than the dose required to resolve WITHDRAWAL
- To address co-occurring PAIN, split daily dose to TID or QID [1]
- For STRESS-RELATED cravings, consider CLONIDINE 0.1mg TID (scheduled or PRN) [2]
- For co-occurring ALCOHOL USE DISORDER: don't use Naltrexone, but do consider treatment with ACAMPROSATE (FDA-approved) or TOPIRAMATE (off-label)
- >40% of OUD patients also have PTSD [3], so ask about symptoms and consider use of SSRI/SNRI, MIRTAZAPINE, PRAZOSIN (for nightmares), TRAZODONE (for insomnia), counseling referral

1. Alford D, et al. Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. *Annals of Internal Medicine.* Jan 2006; 144(2): 127-134.
2. Kowalczyk W. et al. Clonidine Maintenance Prolongs Opioid Abstinence and Decouples Stress From Craving in Daily Life: A Randomized Controlled Trial With Ecological Momentary Assessment. *American Journal of Psychiatry.* August 2015; 172(8): 761-767.
3. Lopez-Martinez A. Et al. Chronic pain, PTSD and Opioid Intake: a systematic review. *World J Clin Cases* Dec 2019; 7(24): 4254-4269.

Buprenorphine for Pain

Well tolerated, can improve pain scores and affective symptoms

Chong J, et al. Managing long-term high-dose prescription opioids in patients with non-cancer pain: The potential role of sublingual buprenorphine. *Aust J Gen Practice.* Jun 2020; 49(6):339-343.

Safe and efficacious pain treatment for patients with SUD or high-risk opioid overuse/misuse; 6-year data set

Kaski S, et al. Sublingual Buprenorphine/Naloxone and Multi-Modal Management for High-Risk Chronic Pain Patients *Journal of Clinical Medicine.* March 2021; 10(5)

Significant advantages over other opioids used for chronic pain: better safety profile and tolerability. Less likely to lead to hyperalgesia.

Rudolf G. Buprenorphine in the Treatment of Chronic Pain. *Phys Med Rehabil Clin N Am.* May 2020; 31(2):195-204.

33 studies reviewed; all 33 showed efficacy for buprenorphine in pain relief

Pergolizzi J, Raffa R. Safety and Efficacy of the Unique Opioid Buprenorphine for the Treatment of Chronic Pain. *Journal of Pain Research.* December 2019;12:3299-3317.

Severe Opioid Intoxication / Overdose

Assume opioid intoxication if patient presents with:

- nodding off or unconsciousness

- confused/disoriented

- respiratory depression

- meiosis

In this case consider use of Naloxone (Narcan)

- nasal atomizer delivers 4mg; repeat every 2-3 minutes if no response

- and call EMS

New Mexico law requires prescribing of Naloxone with all opioid prescriptions

Questions or Discussion