

New Data: Buprenorphine and Benzodiazepine Overdose Risk

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Learning objectives

- Be able to discuss how the addition of buprenorphine changes overdose risk
- Be able to discuss affect of buprenorphine on risk for benzodiazepine overdose
- Be able to discuss the use of Clonidine in MOUD treatment

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 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

Buprenorphine + Benzo Overdose Risk

Does overdose risk increase with the combination?

Low dose defined as:

< 3mg of Alprazolam
< 6mg of Lorazepam
< 3mg of Clonazepam
< 30mg of Diazepam

- Buprenorphine treatment vs non-treatment days
40% reduction in poisoning events (OR=0.63)
- Poisoning Odds Ratios for benzodiazepine or Z-drug treatment without buprenorphine:
low dose Benzo or Z-drug: **OR=1.69**
high dose Benzo or Z-drug: **OR=2.23**
- Low-dose Benzo or Z-drug treatment + buprenorphine: **OR=1.11**
- High-dose Benzo or Z-drug treatment + buprenorphine: **OR=1.64**

MOUD Reduces Risk of Overdose Death for Patients with Opioid Use Disorder

Retrospective treatment data linked to death records:

- Study included 48,000 patients in outpatient treatment for OUD
- MOUD treatment associated with substantially reduced risk (HR=0.18)
- **82%** reduced risk of death while treated compared to when not treated
- Risk reduction was only present while in treatment - not after discontinuation

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

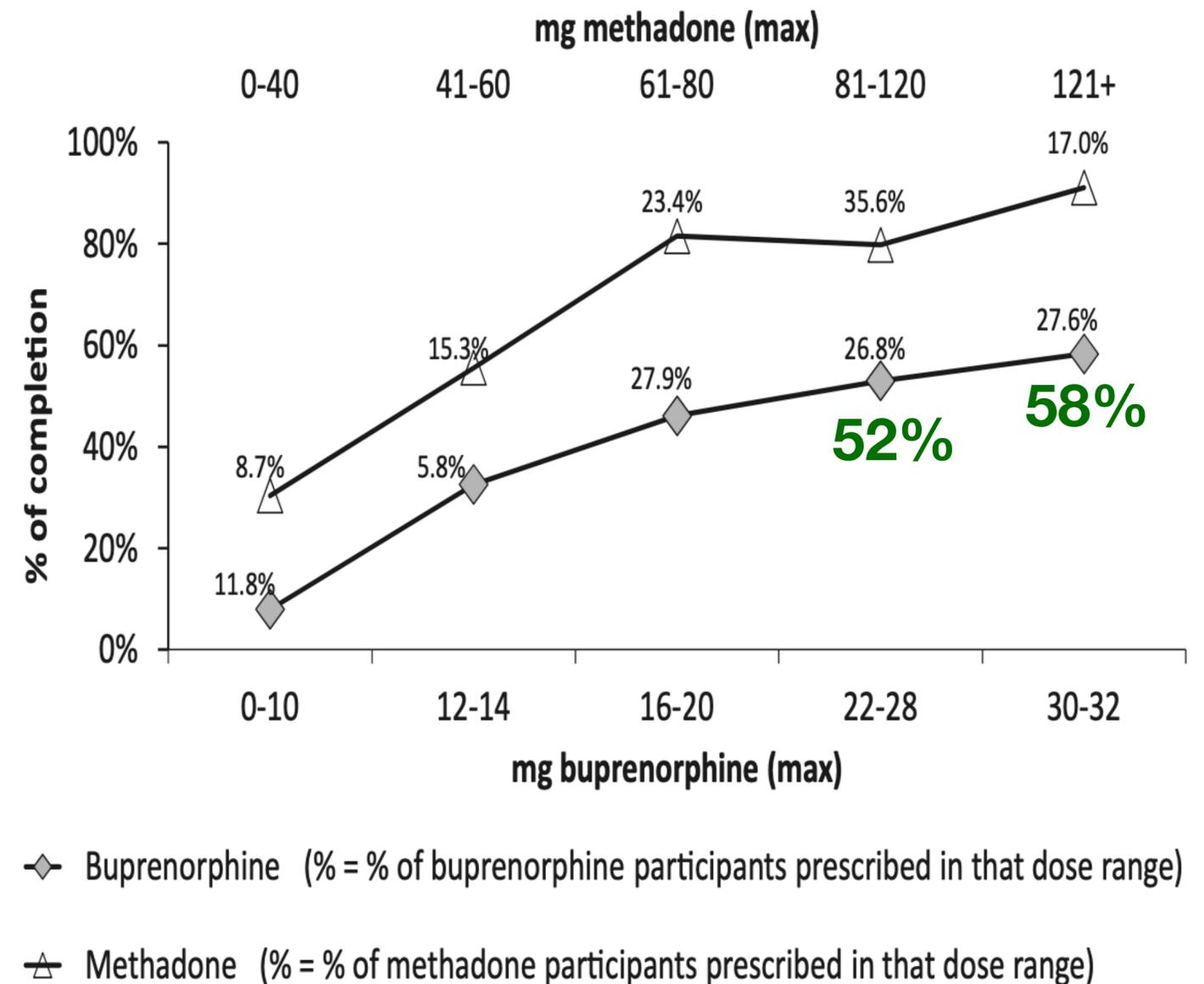


Figure 2 Comparing retention at 24 weeks by maximum dose of medication prescribed

Clonidine for Stress-Related Opioid Cravings

- Clonidine can be added in cases where MOUD is being used, but stress-related opioid cravings remain problematic
- Clonidine can be started at 0.1mg TID (scheduled or PRN, based on patient's need and preference).
- This can be an alternative to increasing Buprenorphine dose in some cases

1. 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.
2. Kowalczyk W, et al. Using ecological momentary assessment to examine the relationship between cravings and affect with opioid use in a clinical trial of clonidine as an adjunct medication to buprenorphine treatment. *The American Journal of Drug and Alcohol Abuse*. August 2018; 44: 502-511

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 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 ², 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. Lopez-Martinez A. Et al. Chronic pain, PTSD and Opioid Intake: a systematic review. *World J Clin Cases* Dec 2019; 7(24): 4254-4269.