MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Polysubstance Use Disorders

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Faculty Disclosure

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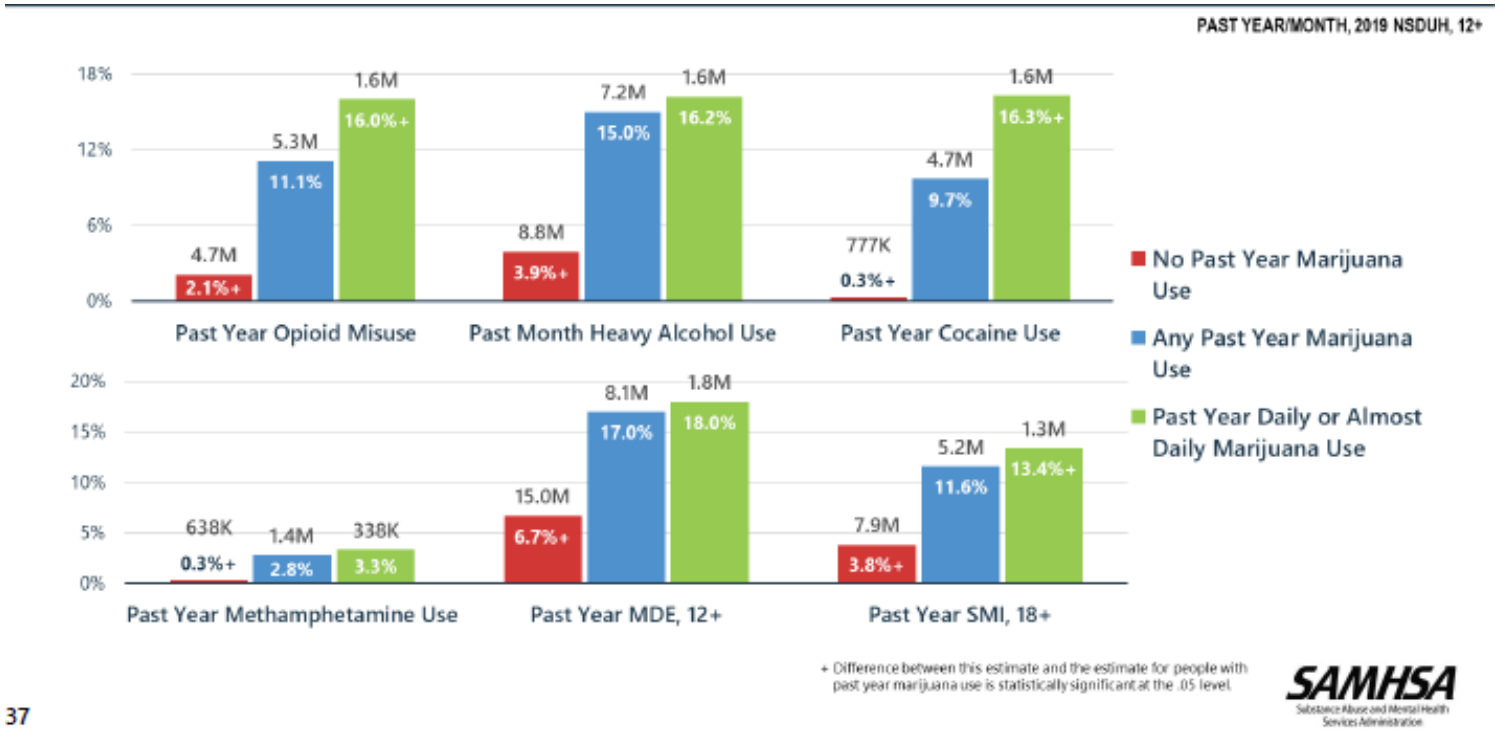
- **Arbor, Otsuka, NIH (NIDA), Ironshore, Vallon**
- **Licensing agreement with Ironshore (Before School Functioning Questionnaire)**
- **Clinical care: MGH, Bay Cove Human Services, Gavin/Phoenix, National Football League (ERM Associates), Major/Minor League Baseball**
- **(Co)Edited Straight Talk About Psychiatric Medications for Kids (Guilford); ADHD Across the Lifespan (Cambridge) , MGH Comprehensive Clinical Psychiatry (Elsevier), MGH Psychopharmacology and Neurotherapeutics (Elsevier)**
- **Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (eg, substance use disorders)**

Marijuana misuse/disorder is Frequently Observed with other SUD



MDE= moderate mental illness; SMI=Severe mental illness
https://www.samhsa.gov/sites/default/files/substance-use-disorder-best-practices-09232019.pdf

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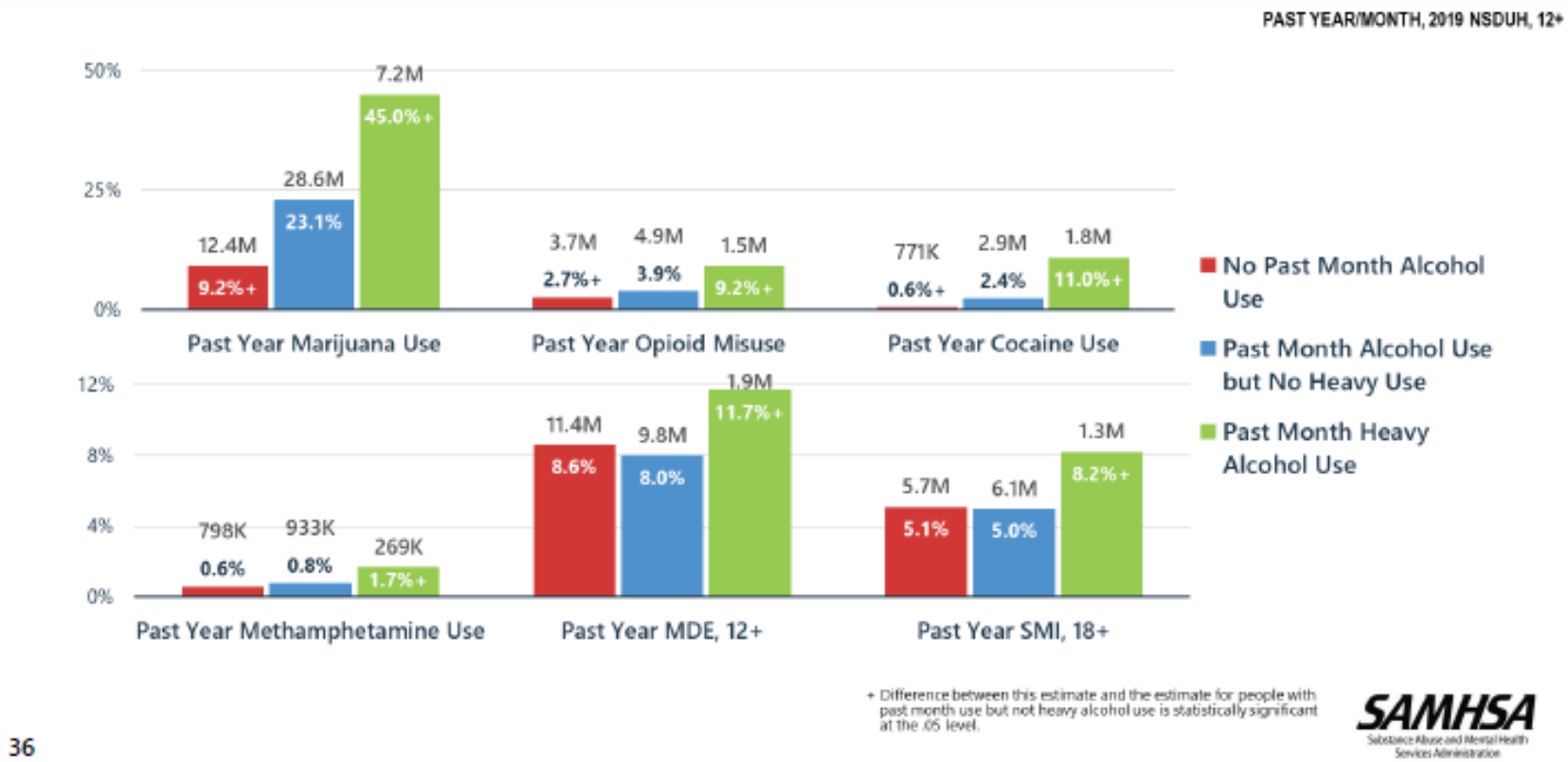
Alcohol misuse/disorder is Frequently Observed with other SUD



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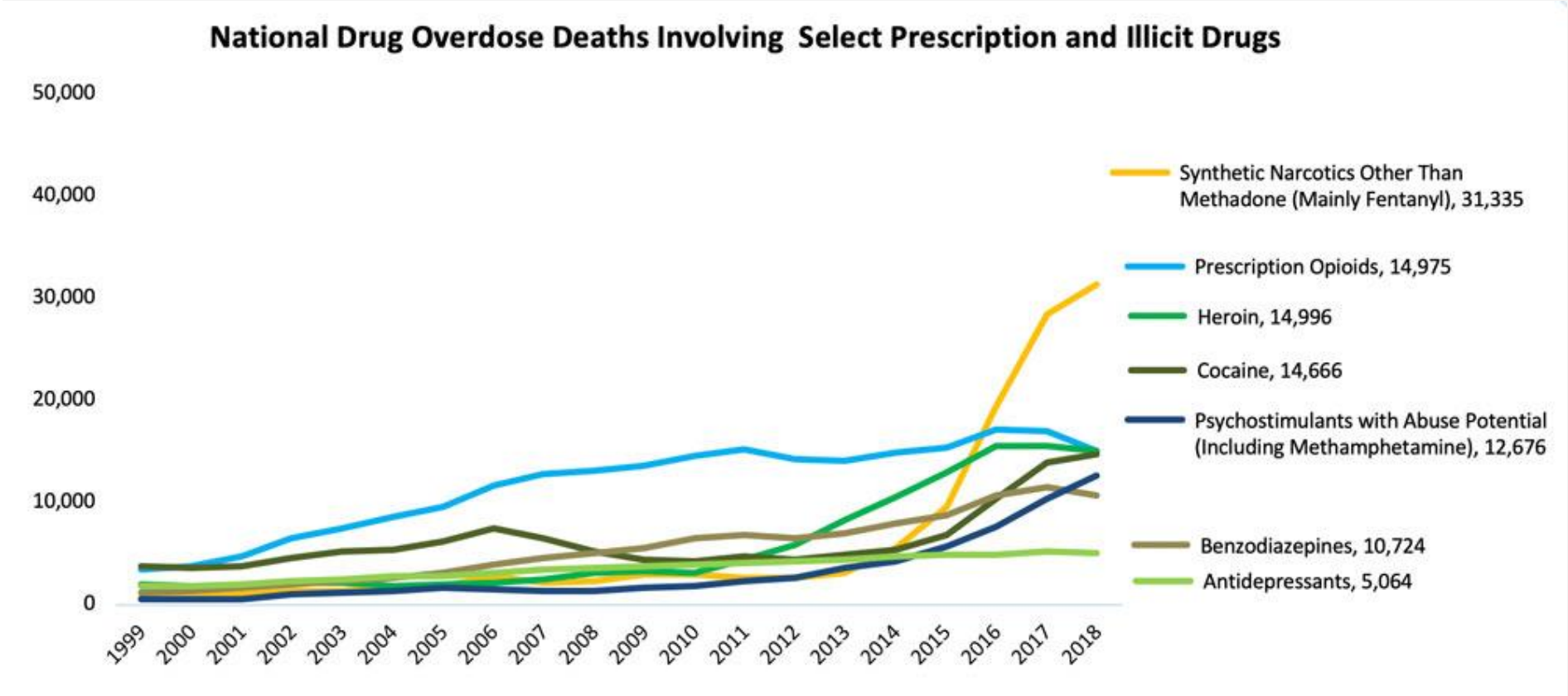
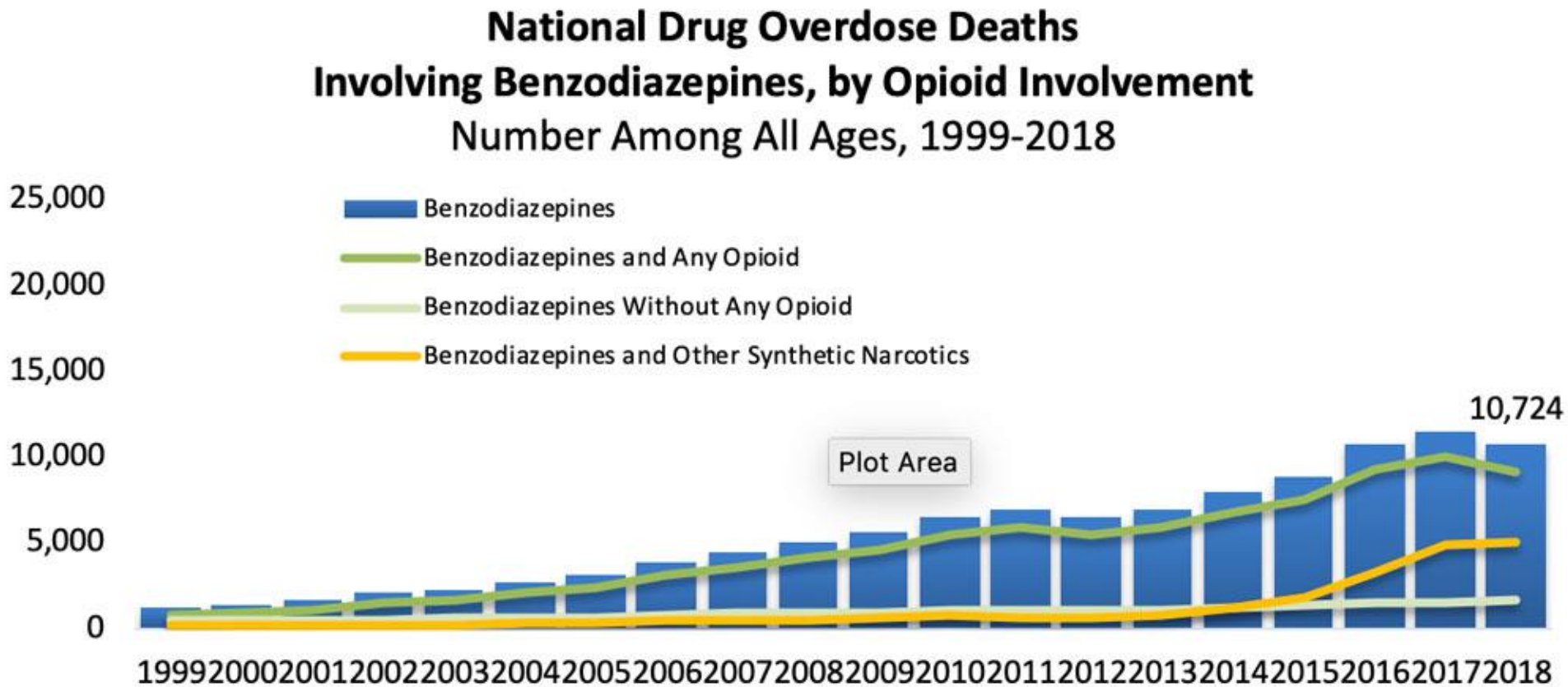
score



https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates



https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates

Longer Term Outcomes of Tranquilizer Use (e.g. Benzodiazepines; BZP) in Middle Aged Americans

- **Design: Up to 15 year Monitoring the Future longitudinal study of 19,209 HS students**
- **Focus on medical and medical+misuse of tranquilizers (e.g. BZP)**
- **Findings (Age 35 to 50 years old):**
- **At age 35, 30% used BZP: 11% medically only, 7.9% medically + misuse, and 12% misuse only**
- **Among those with medical BZP use at age 35:**
  - **11% developed prescription BZP misuse**
  - **42% developed two or more SUD symptoms**
- **BZP misuse was associated with an even higher SUD risk**

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McCabe et al., 2021 (submitted)

Massachusetts Overdose Data (June 2020)

- **Largely fentanyl > opioids**
- **Additional substances common**
  - **Cocaine: 40%**
  - **Benzodiazepines: 33%**
  - **Amphetamines 10%**
  - **Other-unclear since not always evaluated**
- **Older study of "deaths on street" (O'Connell unpublished)**
  - **2/3 of deaths associated with clonidine, clonazepam, gabapentin, opioids**

Alprazolam + Alcohol

- **Reported increase in overdoses including death with combination**
  - **Typically in patients with SUD**
- **Additive sedative effects of alprazolam plus EtOH**
- **Increased behavioral aggression with the combination**
- **Alprazolam metabolism altered in context to alcohol**
  - **In vivo studies show up to 600% increase in brain alprazolam with EtOH (3 g/kg)**
  - **May have inhibition of 3A4 metabolism**

Bond and Silviera, J Stud alcohol Suppl 1993 11:30-35; Huang et al.Expert OpinDrug Metab Toxicol 2018: 14:551-9 ; Darket et al, Drug Alc Dep 2014: 138:61-6

BZP Prescribing Patterns and Death in Veterans Receiving Opioids: Case Controlled Study

To study the association between benzodiazepine prescribing patterns including dose, type, and dosing schedule and the risk of death from drug overdose among US veterans receiving opioid analgesics.
Design: Case-cohort study.

Setting: Veterans Health Administration (VHA), 2004-09.
Participants: US veterans, primarily male, who received opioid analgesics in 2004-09. All veterans who died from a drug overdose (n=2400) while receiving opioid analgesics and a random sample of veterans (n=420,386) who received VHA medical services and opioid analgesics.

Main outcome measure: Death from drug overdose, defined as any intentional, unintentional, or indeterminate death from poisoning caused by any drug, determined by information on cause of death from the National Death Index.

Results: During the study period 27% (n=112,069) of veterans who received opioid analgesics also received benzodiazepines. About half of the deaths from drug overdose (n=1185) occurred when veterans were concurrently prescribed benzodiazepines and opioids. Risk of death from drug overdose increased with history of benzodiazepine prescription: adjusted hazard ratios were 2.33 (95% confidence interval 2.05 to 2.64) for former prescriptions versus no prescription and 3.86 (3.49 to 4.26) for current prescriptions versus no prescription. Risk of death from drug overdose increased as daily benzodiazepine dose increased. Compared with clonazepam, temazepam was associated with a decreased risk of death from drug overdose (0.63, 0.48 to 0.82). Benzodiazepine dosing schedule was not associated with risk of death from drug overdose.

Conclusions: Among veterans receiving opioid analgesics, receipt of benzodiazepines was associated with an increased risk of death from drug overdose in a dose-response fashion.

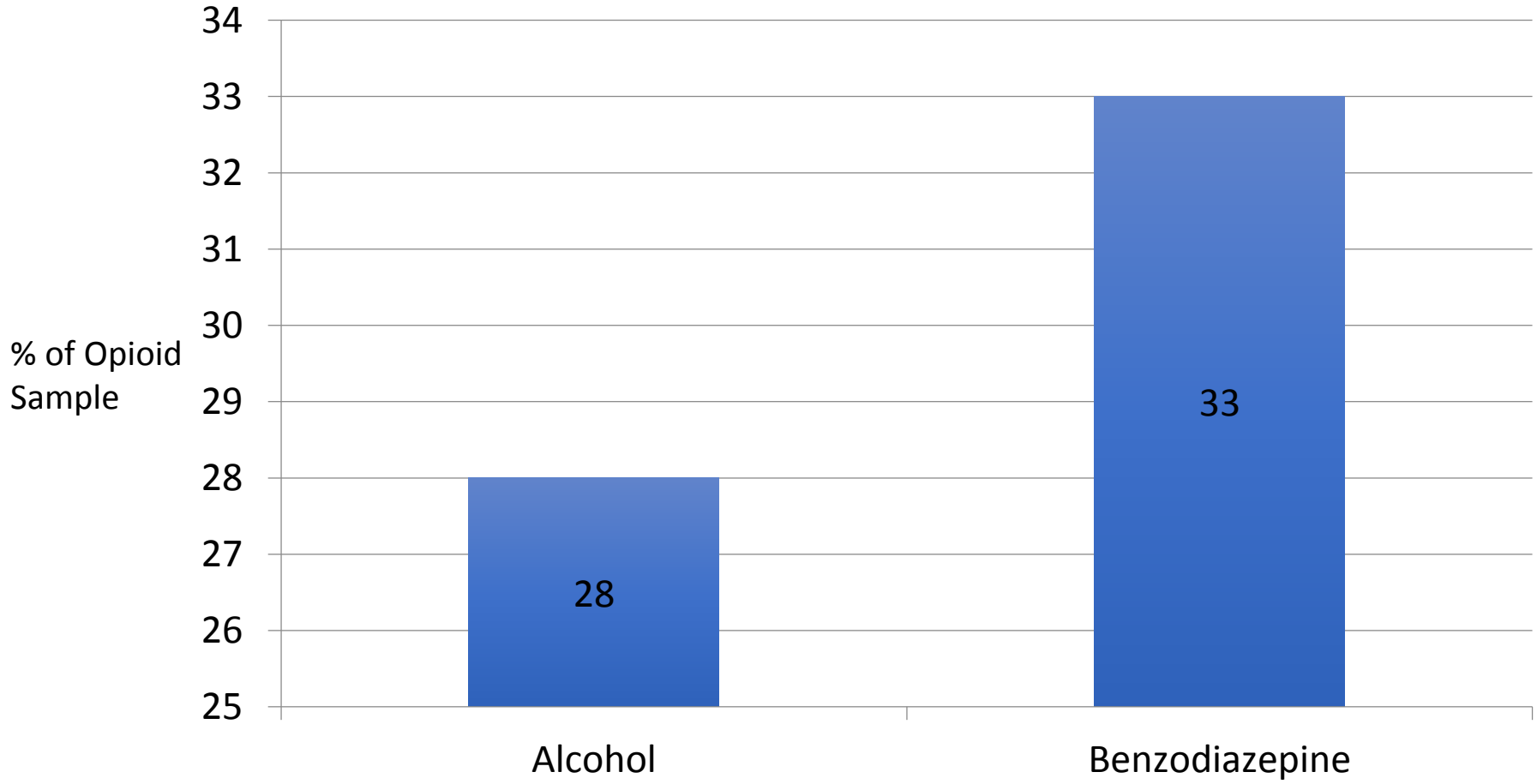
Park et al., BMJ. 2015 Jun 10;350

Study of Polysubstance Misuse in Opioid Dependent Patients Seeking Detoxification: Characteristics (N=162)

- **Sample: N=162 patients seeking opioid or alcohol detoxification in a public detoxification unit (BayCove Human Services)**
- **Age**
  - **Mean age 33 years**
  - **Range 18-62 years**
- **Gender**
  - **82 Males (51%)**
- **Onset of SUD**
  - **Mean onset of 16 years of age**
  - **Range 7-34 years of age**
- **Use of self-report questionnaires on admissiom**

Wilens et al. Am J Addict 2015;24:173–177

Opioid Dependent Patients Seeking Detoxification Often Require Additional Withdrawal Protocols



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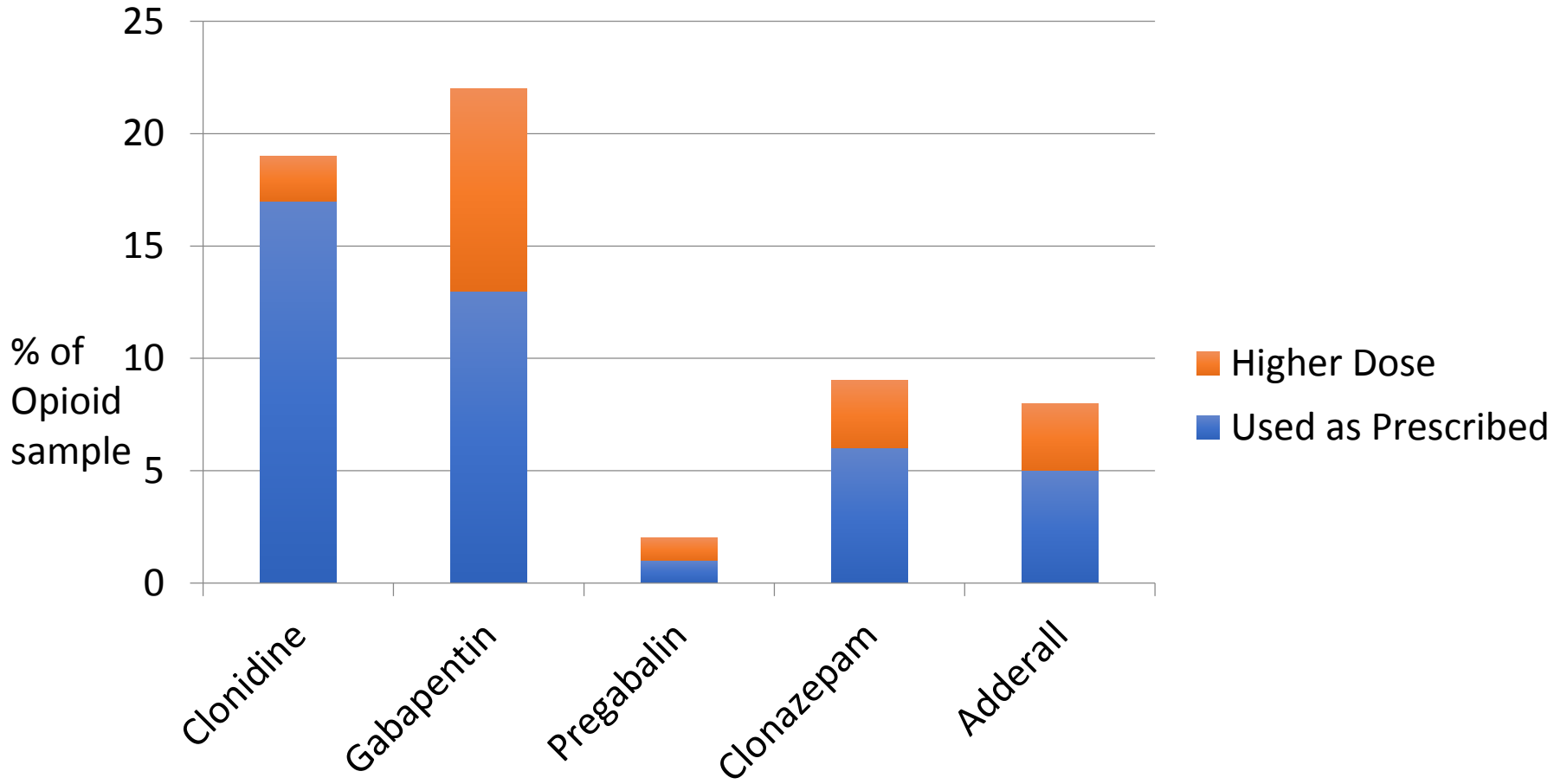
Use & Misuse of Prescription Medications in Opioid Dependent Patients Seeking Detoxification (N=162)



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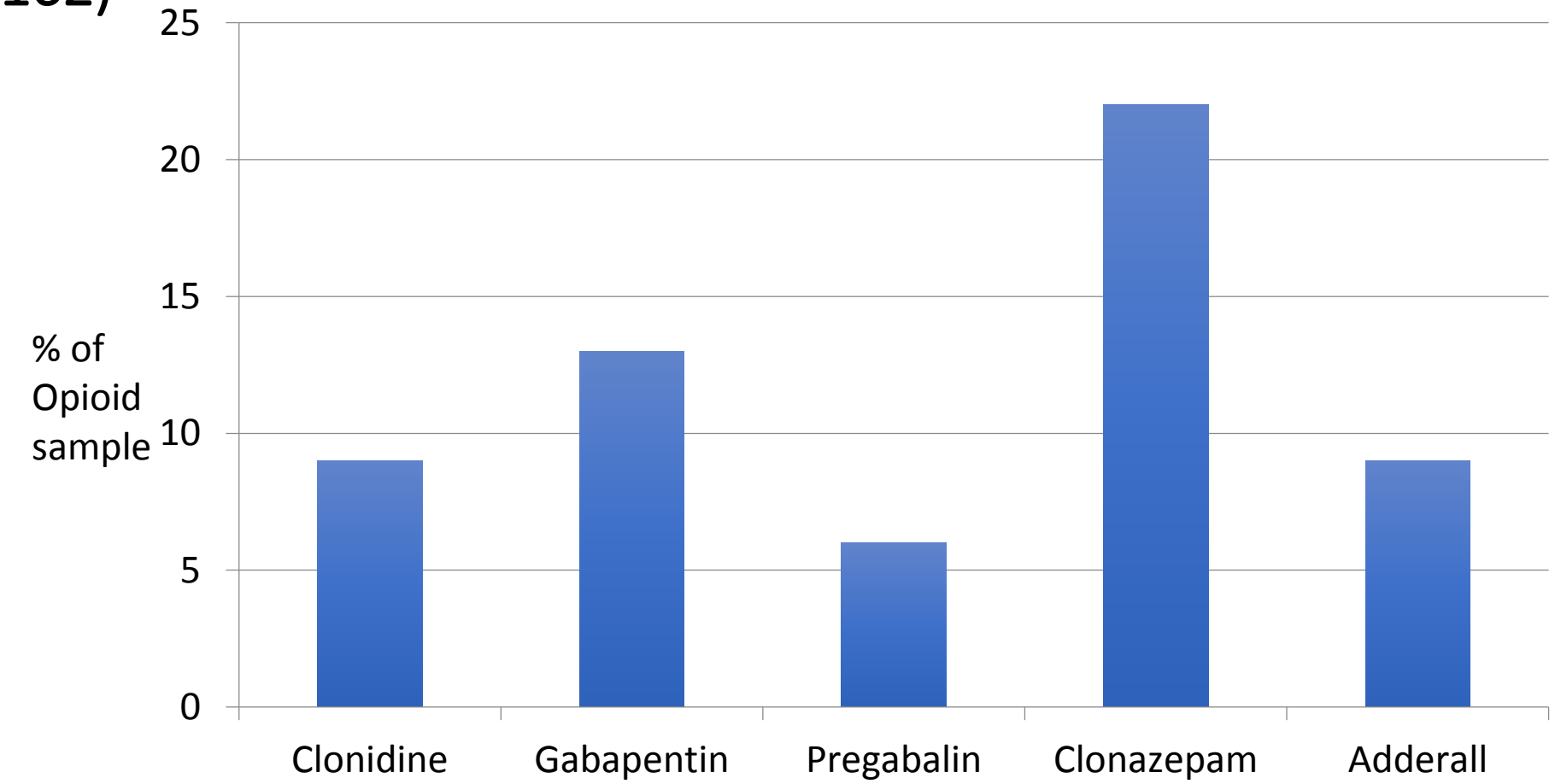
Wilens et al. Am J Addict 2015;24:173–177

Use of Prescription Medication without a Prescription in Opioid Dependent Patients Seeking Detoxification (N=162)



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Gabapentin

- **Mechanism: GABA analog, multiple mechanisms, inihibition of voltage Ca channels**
- **FDA Approved for seizures**
  - **Efficacy for alcohol cessation > pain > mood**
- **Prevalence of misuse: 1% general population, 20-30% SUD Tx Centers**
- **Similar pattern to controlled substances in terms of misuse**
  - **Three times FDA approved dose**
  - **Street value**
  - **Increasingly schedule V by state jurisdiction – in PMP**
- **Use with opioids**
  - **Increases likelihood of respiratory depression 4- fold**
  - **One analysis: typically 3 gm/day taken with opioids**
  - **Creates excessive sedation, increases opioid euphoria & duration of action**
- **Withdrawal usually within 2 day; low level, nonfatal, similar to sedative w/d**

Wilens et al. Am J Addict 2015; Peckman A et al, Risk Mgmt Healthcare Policy 2018:11L 109-116; Mersfelder and Nichols, Ann Pharmacol 2016:50:229-33

Clonidine

- **Clonidine is an alpha agonist**
  - **Negative chronotrope & ionotrope**
  - **Reduces systemic vascular resistance**
- **FDA approved for blood pressure & ADHD**
- **Shown to be variably effective for anxiety disorders**
  - **N=23 patients, > placebo, 17% worsened anxiety**
  - **N=18 patients, =placebo**
- **Minimal – moderate evidence of efficacy in tics> opioid detox > insomnia > akathisia > PTSD**

Hoen Sarich et al., Arch Gen Psych 1981: Uhde et al. Arch Gen Psych 1989
Naguy, Pharmacology 2016: 98:87-92

Clonidine plus opioids

- **Useful in opioid withdrawal**
  - **Lower retention & higher rate of relapse vs opioid therapy**
  - **Lofexidine FDA approved for opioid w/d- fewer side effects than clonidine**
- **Anecdotally boosts effects and duration of opioids and other substances (e.g. sedatives)**
- **Concerns with rebound hypertension during abrupt discontinuation**
  - **Elevated systolic/diastolic BPs (e.g. 190s/100's)**
  - **Slow heart rate/ bradycardia (e.g. 50's-60's)**
  - **Treat with low dose clonidine then taper (e.g. 0.1 mg TID then BID then QD)**
- **May be additive to fatalities in overdose (limits compensatory response)**

Gold et al., JAMA 1980; Dennison Psychiatric Q: 2001:72:191-5; O'Connell J-personal communication

Summary

- **Polysubstance misuse/use disorder is common**
- **Alcohol > marijuana most frequent co-used substances with other SUD**
- **Prescription medications frequently misused with opioids and other substances of misuse**
- **Benzodiazepines frequently implicated with (fatal) opioid overdoses**
- **Clonidine & Gabapentin are misused frequently in context to SUD**