Safe Use of Benzodiazepines: Clinical, Regulatory, and Public Health Perspectives

July 12 & 13, 2021

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

Welcome & Overview | Day 1

Mark McClellan

Duke-Margolis Center for Health Policy

Meeting Agenda

Day One

- Session 1: Benzodiazepine Abuse Liability, Epidemiology, and Clinical Considerations
- Session 2: Clinical, Pharmacologic, and Public Health Perspectives

Day Two

- Session 3: Health Professional and Patient Advocate Perspectives – Best Practices, Experiences, and Concerns
- Session 4: Balancing the Benefits and Risks of Benzodiazepines

Virtual Meeting Reminders

- Visit the Duke-Margolis website (https://healthpolicy.duke.edu/events) for meeting materials, including the agenda, speaker biographies, and discussion topics.

- Questions for our panelists? Feel free to submit questions via Zoom's Q&A function.

- Join the conversation @Duke-Margolis #SafeUseBenzodiazepines

Opening Remarks from FDA

Douglas Throckmorton

U.S. Food and Drug Administration

Session 1: Benzodiazepine Abuse Liability, Epidemiology, and Clinical Considerations

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy

Chad Reissig

U.S. Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

Pharmacology and Abuse Liability Considerations of Benzodiazepines

Chad J. Reissig, PhD,

Controlled Substance Staff (CSS)

Overview

- Brief review of benzodiazepines
- Pharmacology of benzodiazepines
  - Mechanism of action and receptor binding profile
  - Nonclinical, in vivo, abuse liability data
  - Clinical pharmacology
  - Clinical abuse liability data
  - Dependence/withdrawal-related data
- Conclusions

Benzodiazepines

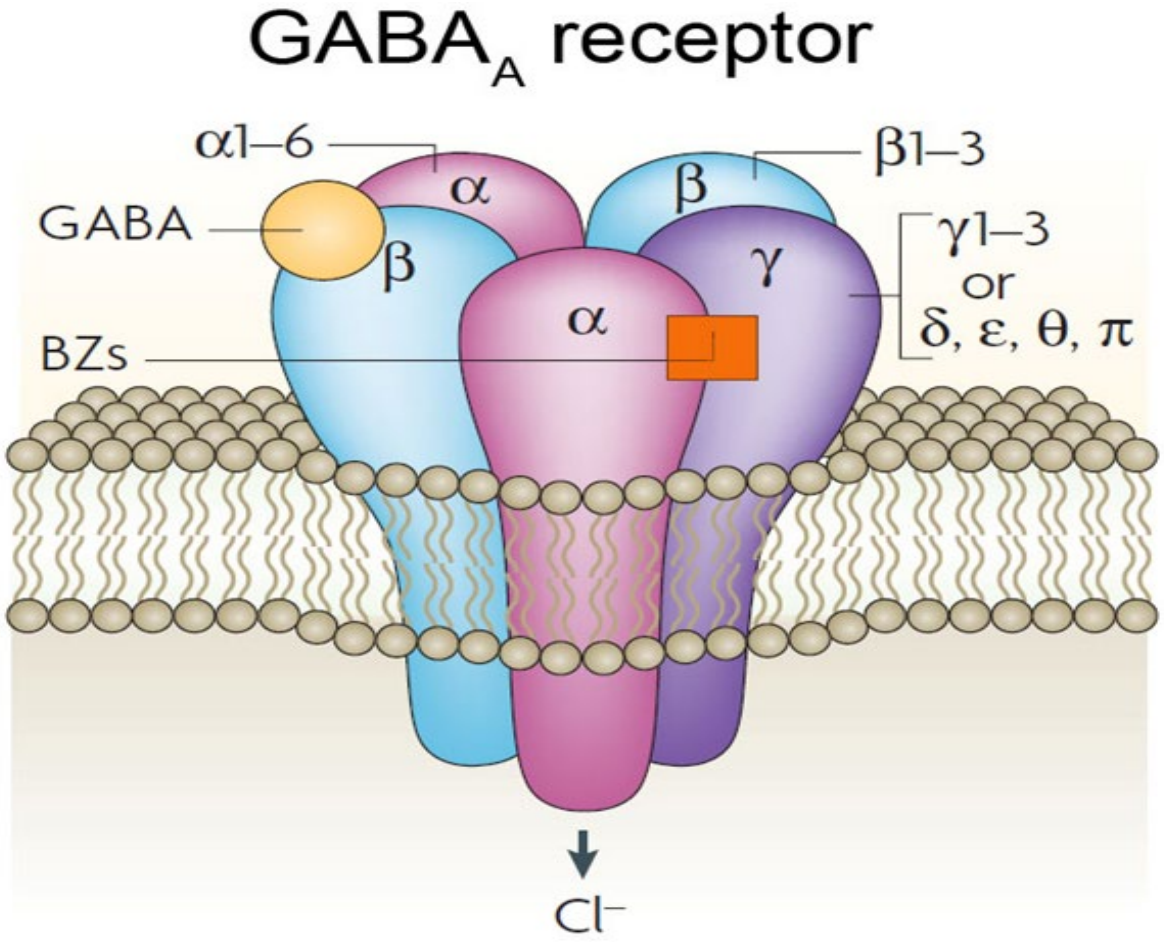
- Have been used clinically for more than 50 years in a variety of indications
  - For example, alprazolam was approved on October 16, 1981 for the management of generalized anxiety disorder, panic disorder, or the short-term relief of symptoms of anxiety
- At least 24 benzodiazepine substances have been approved, with close to 1,000 currently marketed formulations
- Recently, FDA has undertaken a review of the abuse potential of alprazolam

Benzodiazepine Pharmacology

- Benzodiazepines act as positive allosteric modulators at gamma-aminobutyric acid (GABA) receptors; they increase the affinity of GABA receptors for GABA and promote its binding
  - GABA is the most common inhibitory neurotransmitter in the central nervous system and decreases neuronal activity
- Any differences in binding affinity for $GABA_A$ receptors across the benzodiazepine class does not impart meaningful clinical differences

Benzodiazepine Pharmacology

- The $GABA_A$ receptor is a ligand-gated ionotropic channel
- $GABA_A$ receptors are pentameric transmembrane receptors that consist of five subunits arranged around a central pore
- Each of the subunits have multiple isoforms (e.g., six alpha isoforms, three beta isoforms, and three gamma isoforms) which leads to a large number of different $GABA_A$ receptors

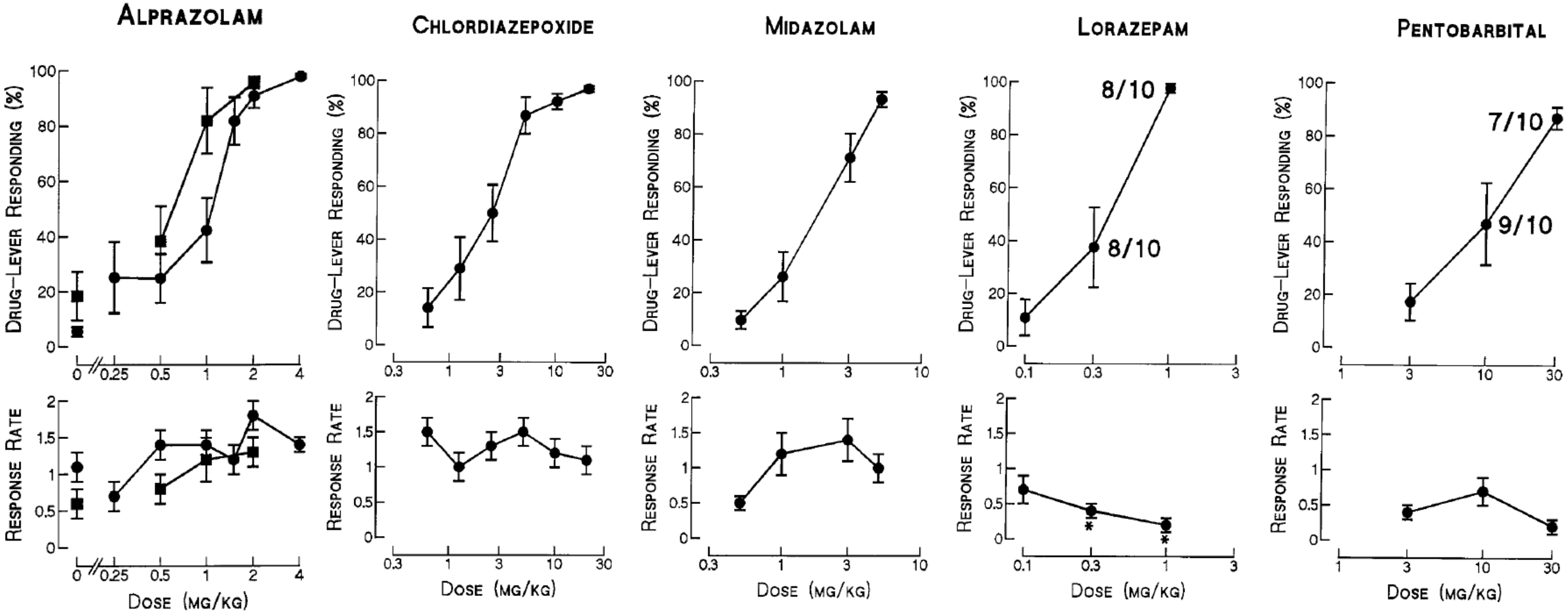


Jacob et al., Nature Reviews Neuroscience, 2008

Preclinical pharmacology

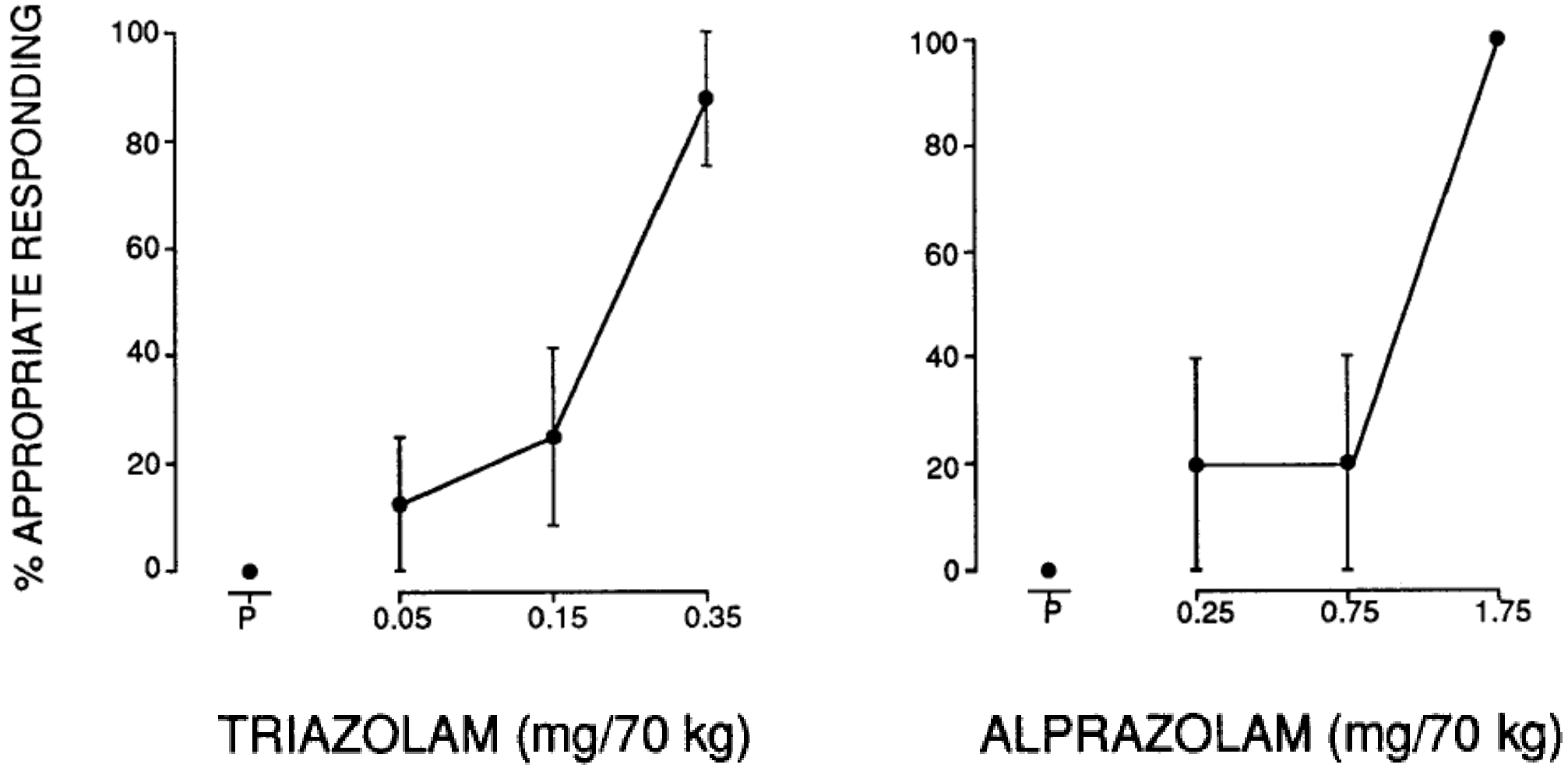
- ***Drug discrimination*** is an experimental method in which animals identify whether a test drug produces physical or behavioral effects (an interoceptive response) similar to those produced by another drug with known pharmacological properties
  - It is often used as a model of the subjective effects of drugs

Drug Discrimination - Rodents



Gommans, J., Hijzen, T.H., Maes, R.A., and Olivier, B. (2000). Discriminative stimulus properties of alprazolam. Psychopharmacology (Berl) 148, 146-152

Drug Discrimination - Humans



Smith, B.J., and Bickel, W.K. (2001). Effects of alprazolam, caffeine, and zolpidem in humans trained to discriminate triazolam from placebo. Drug and alcohol dependence *61*, 249-260.

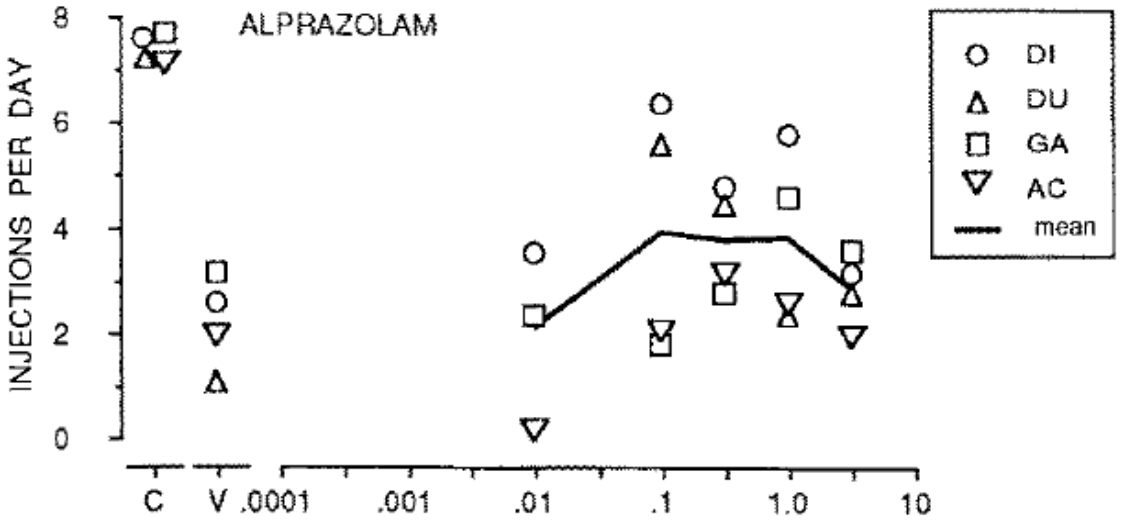
Drug Discrimination - Summary

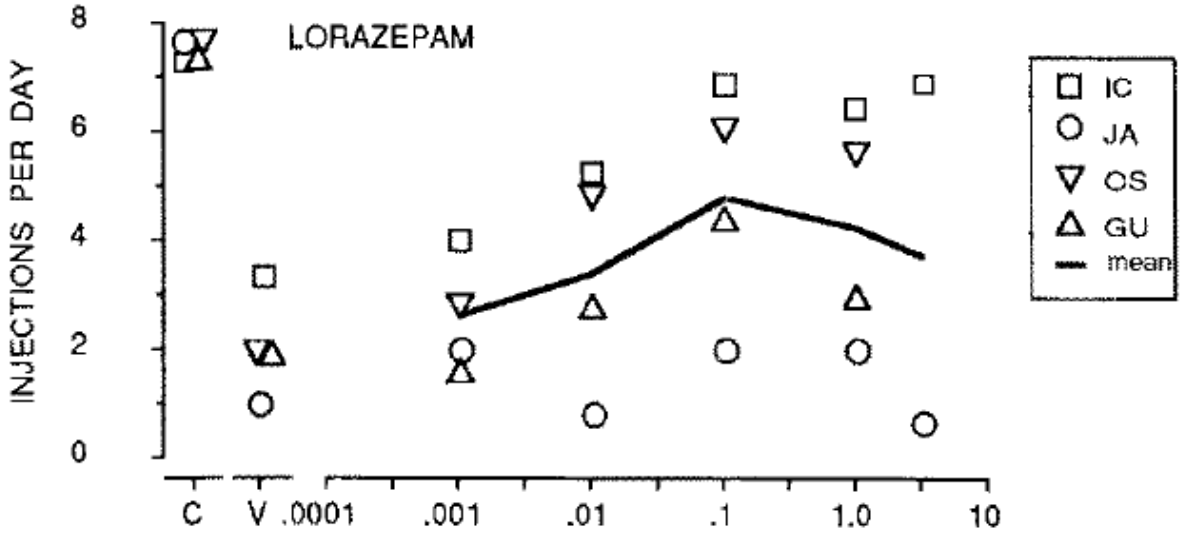
- Consistent with their shared mechanism(s) of action, the benzodiazepines substitute for one another in drug discrimination studies (i.e., produce symmetrical, and/or cross generalization)
  - This suggests similarity in their subjective effects profile

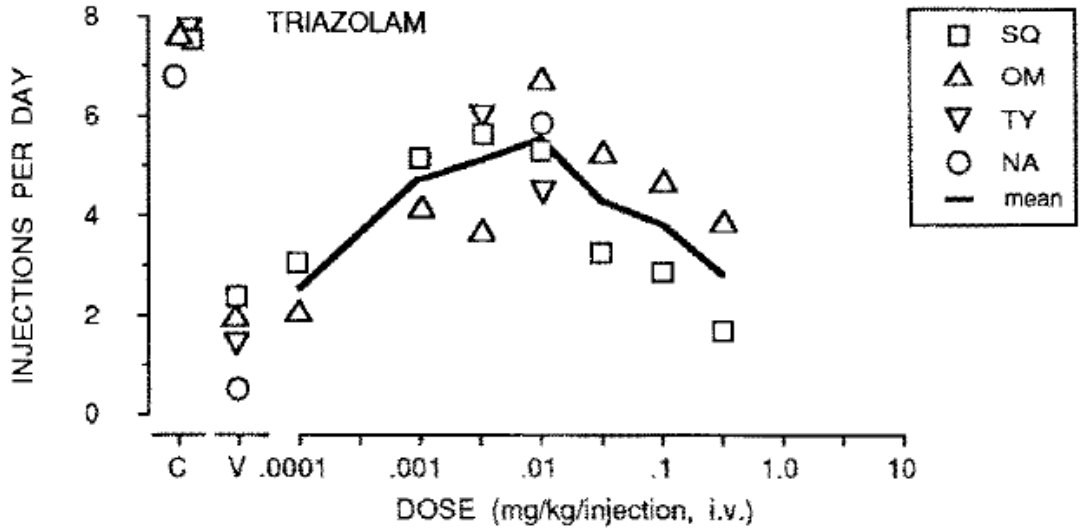
Self-administration

- ***Drug self-administration*** is an experimental method in which animals directly identify if a substance has positive reinforcing effects
- In this procedure, animals are trained to press a lever a set number of times (i.e., a fixed-ratio) resulting in the intravenous administration of a drug
- If intravenous administration of a drug is reinforcing, an animal will "work" (e.g., bar press) to obtain it

Self-administration







Griffiths, R.R., Lamb, R.J., Sannerud, C.A., Ator, N.A., and Brady, J.V. (1991). Self-injection of barbiturates, benzodiazepines and other sedative-anxiolytics in baboons. Psychopharmacology (Berl) 103, 154-161.

Self-administration

- Benzodiazepines are reinforcing and self-administered by a variety of laboratory animals and under varied schedules of reinforcement
  - These data demonstrate their potential for abuse
  - However, the available self-administration data (using basic FR procedures) are less useful for determining *relative* abuse potential

Clinical Pharmacology

- Benzodiazepines have a shared pharmacology, with some differences in clinical pharmacology with respect to:
  - Pharmacokinetic effects (Tmax, half-life, duration of effects, etc.)
  - Potency

Drug	Tmax (hr)	Elimination Half-Life (hr)	Cmax (ng/mL)	Absolute Bioavailability (%)	Active Metabolite	CYP Interactions	Protein Bound (%)
Alprazolam	1-2	11.2 (6.3-26.9)	8-37 [dose: 0.5-3.0mg]	[IR formulation unavailable; XR formulation 90%]	4-hydroxyalprazolam and alpha-hydroxyalprazolam	CYP3A4	80
Clonazepam	1-4	30-40	n/a	90	Inactive	Limited CYP3A4	85
Lorazepam	2	12[A]-18[B]	20 [dose: 2.0mg]	90	Lorazepam glucuronide	No (hepatic metabolism via conjugation)	85
Diazepam	1-1.5	Up to 48[A]: Up to 100[B]	n/a	>90	N-desmethyldiazepam	Limited CYP3A4; CYP2C19	98
Temazepam	1.2-1.6	8.8 (3.5-18.4)	666-982 [dose: 30mg]	92 (after first-pass metabolism)	Inactive	No (hepatic metabolism via conjugation)	96

Clinical Pharmacology

- Across the class, many of the benzodiazepines have broadly similar PK properties and do not appear to have substantial differences in pharmacodynamic effects

Clinical Studies of Benzodiazepines

- Older clinical studies have examined benzodiazepines using a variety of outcome measures suggestive of abuse liability:

- Orzack et al. (1988) compared alprazolam (2 mg), lorazepam (4 mg), diazepam (20 mg), methaqualone (300 mg, C-II), and placebo
  - All benzodiazepines produced effects on various ARCI subscales
  - “Street value” of the benzodiazepines and likelihood of using again were also assessed

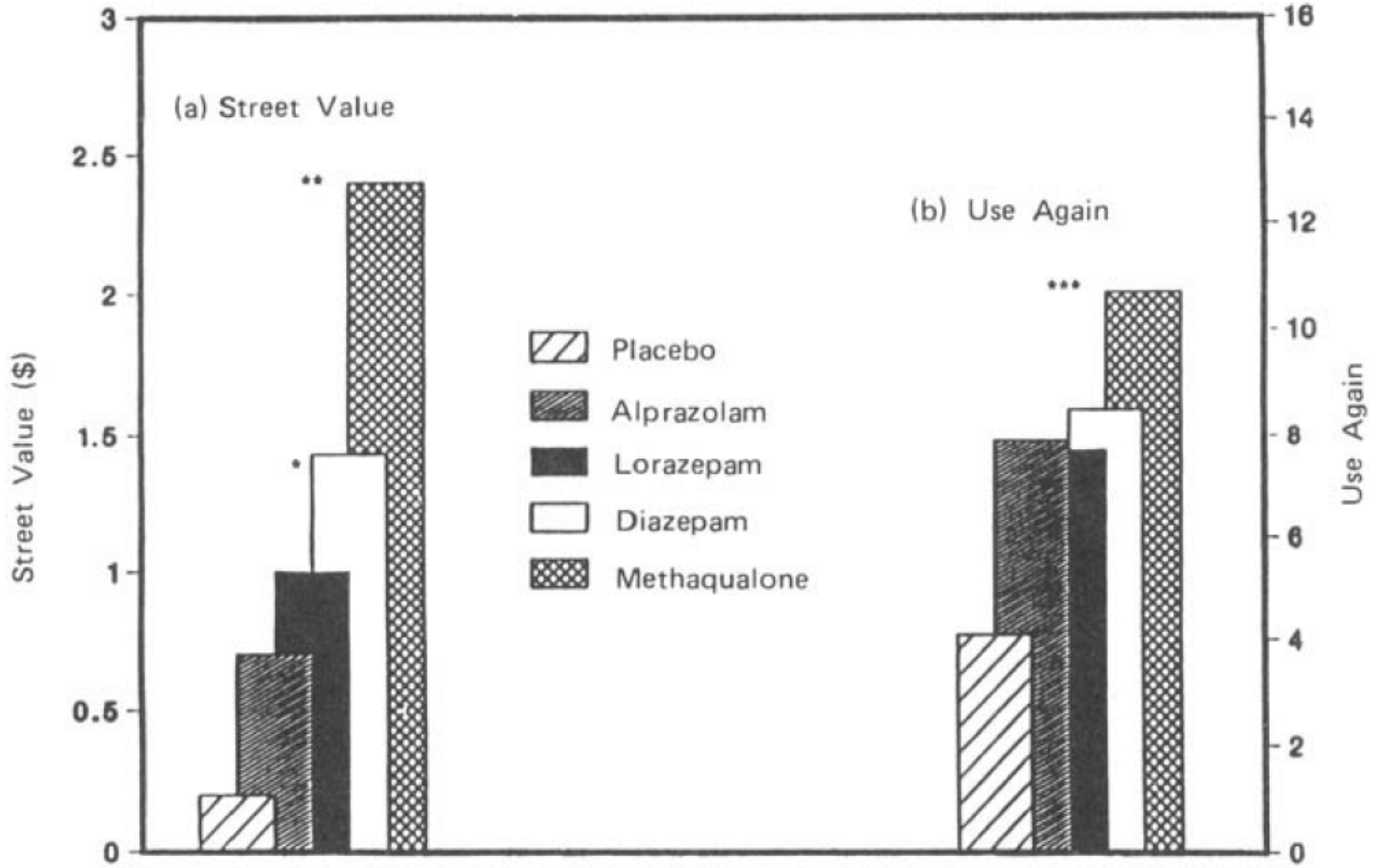
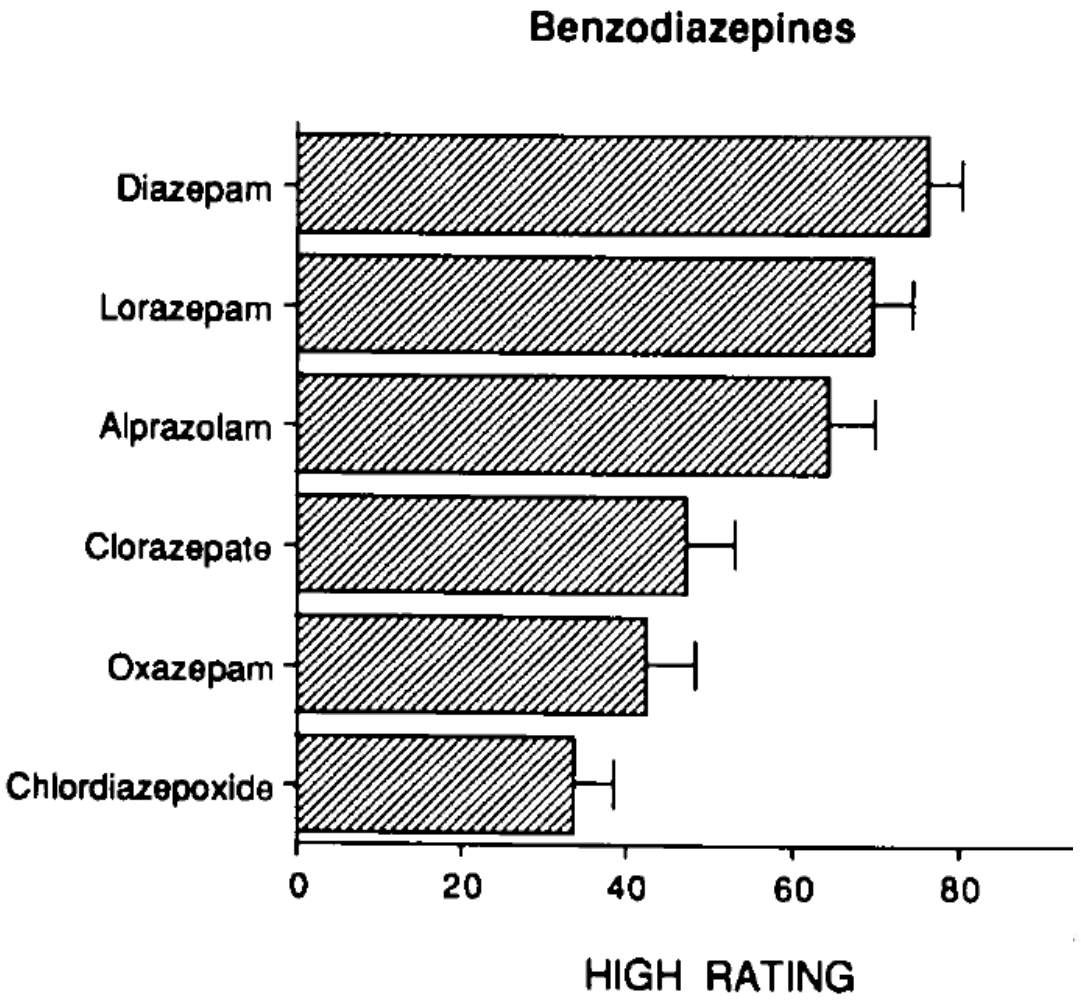


Fig. 3. Street value (a) and use again (b) scales. Street value is plotted monetary value and use again scale is an analogue linear scale ranging from 0 to 16, the latter indicating positive repetition. *Significantly different from placebo and methaqualone ($p \leq .05$). **Significantly different from all treatments ($p \leq .05$). ***Significantly different from alprazolam, lorazepam, and placebo ($p \leq .05$). Ratings taken 1 hour postdrug. All treatments are included in the use again scale.

Clinical Studies of Benzodiazepines

- Busto et al. (1994) compared bretazenil, alprazolam, diazepam, and placebo
  - Psychomotor effects, subjective effects (ARCI, POMS), and observer-rated scales all produced similar results between alprazolam and diazepam
- Griffiths et al. (1991) examined a variety of abuse-related data to explore differences in benzodiazepine abuse liability
  - Self-report ratings of “high” from sedative users and physician ratings of abuse liability suggested that diazepam had the greatest abuse liability



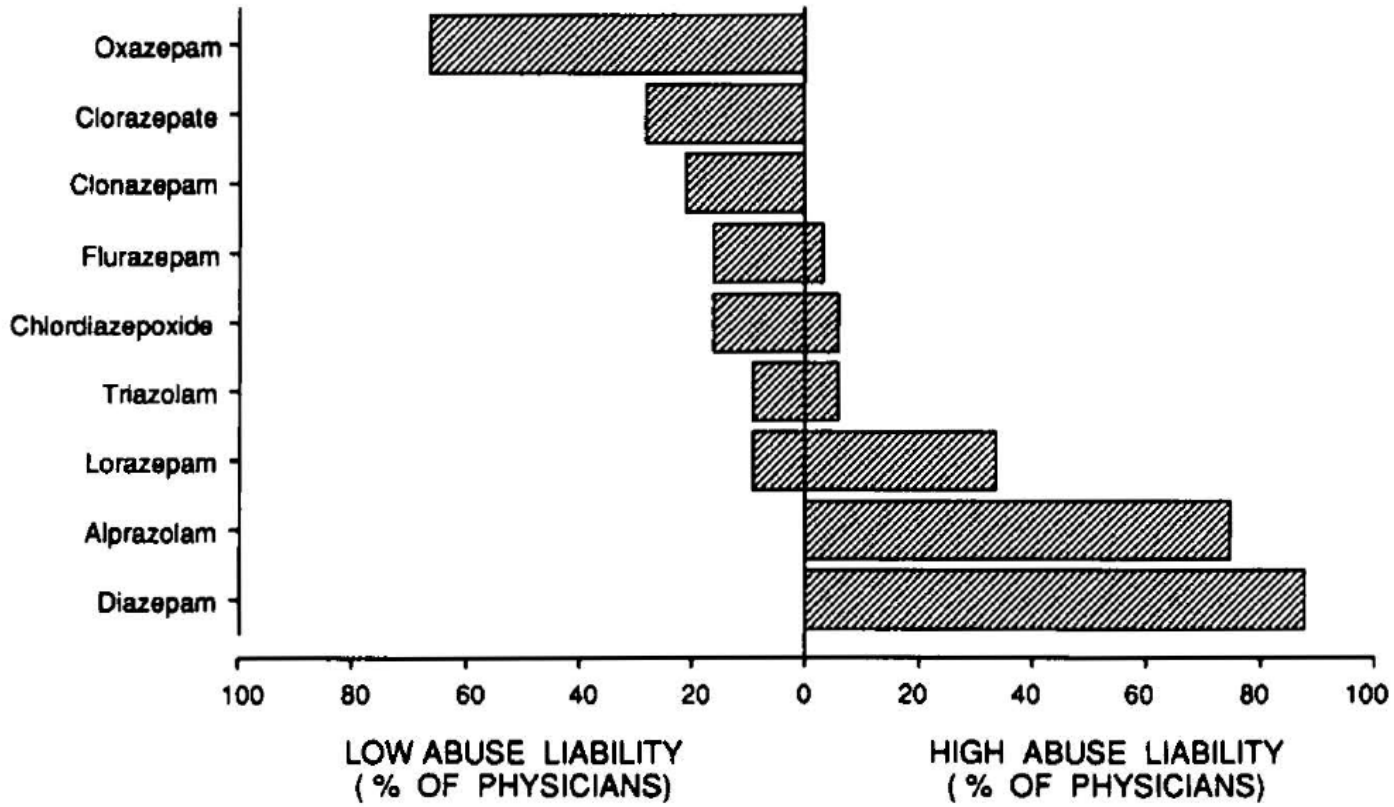


FIG. 2. Drug abuser ratings of relative "high" from various sedatives and benzodiazepines. On a 100-mm line, subjects rated the "high" they typically felt when using each drug (0 = not at all; 100 = extremely). Bars show means and brackets show 1 SEM for samples ranging between 23–40 subjects. Data in the top and bottom panels are from the same question in the structured interview.

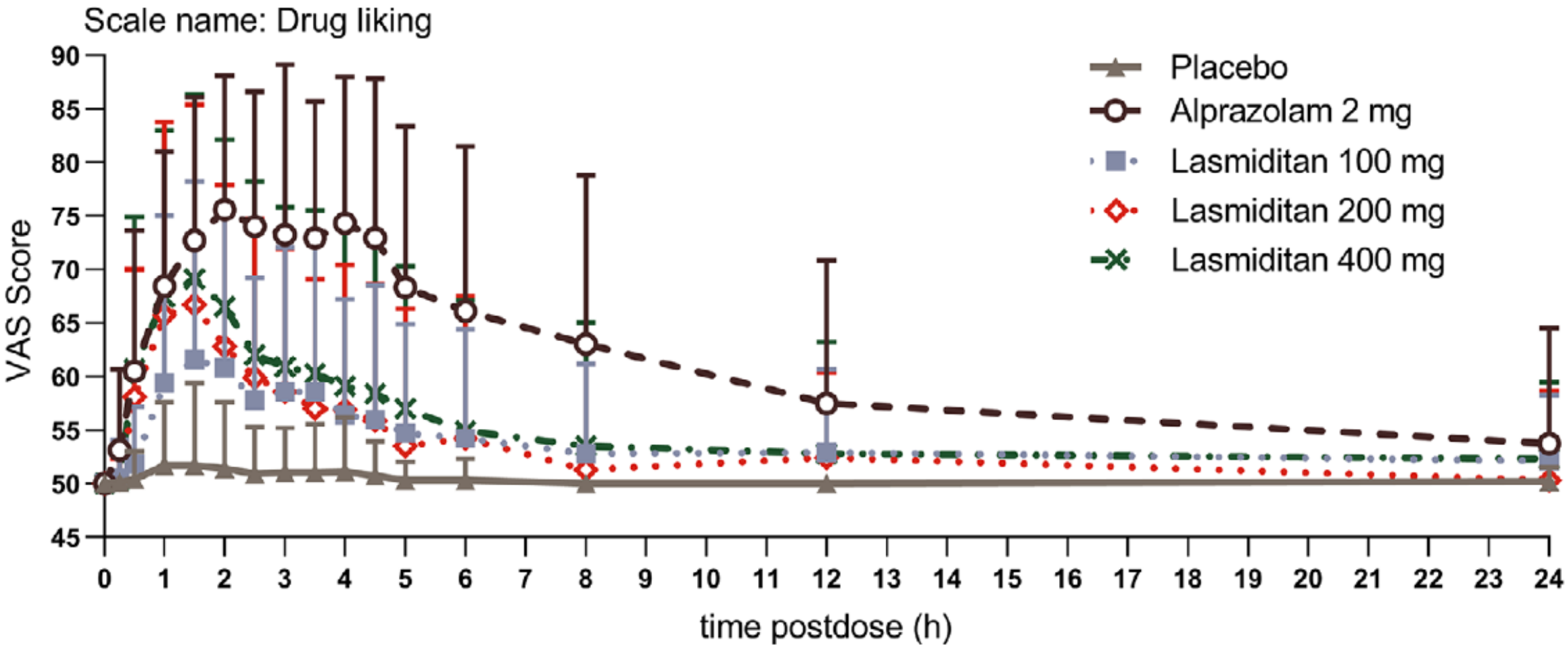
Clinical Studies of Benzodiazepines

- Direct comparisons of benzodiazepines in formal human abuse potential (HAP) studies are lacking
- However, alprazolam has been extensively used in HAP studies as the prototypical comparator for sedative-like drugs

Clinical Studies of Benzodiazepines

- Wilbraham et al. compared 2 mg of alprazolam to lasmiditan (C-V) (100, 200, and 400 mg)
  - Drug liking scores for the high dose of lasmiditan (400 mg) were not significantly different from alprazolam

Clinical Studies of Benzodiazepines



Wilbraham, D., Berg, P.H., Tsai, M., Liffick, E., Loo, L.S., Doty, E.G., and Sellers, E. (2020). Abuse Potential of Lasmiditan: A Phase 1 Randomized, Placebo- and Alprazolam-Controlled Crossover Study. J Clin Pharmacol *60*, 495-504

Clinical Studies of Benzodiazepines

- In a HAP evaluation of brivaracetam (C-V) (50, 200, and 1000 mg), levetiracetam (4000 mg), alprazolam (1.5 and 3 mg), and placebo, both doses of alprazolam produced a level of “drug liking” that was greater than placebo (Schoedel et al, 2018)
  - The intermediate doses of brivaracetam produced similar results to alprazolam on most subjective measures with the 1000 mg dose producing significantly greater levels of drug liking than the highest dose of alprazolam

- In a HAP study comparing lacosamide (C-V) (200 and 800 mg) to alprazolam (1.5 and 3 mg) and placebo, subjective effects of 200 mg lacosamide were significantly lower than alprazolam for “most end points” (Schoedel et al, 2017)
  - The 800 mg lacosamide dose showed a significantly lower “at this moment” Drug Liking visual analog scale (VAS) Emax compared with 3 mg alprazolam, but was not different from 1.5 mg alprazolam

Clinical data - Summary

- Benzodiazepines generally produce “drug liking” and other subjective effects consistent with drugs of abuse

- Though cross-study comparisons are limited, the available clinical data are mixed and have not consistently demonstrated a greater abuse liability of any single benzodiazepine relative to the class

Dependence and Withdrawal

- Following repeated dosing, benzodiazepines and produce physical dependence and withdrawal
- In general, the benzodiazepine class produce similar withdrawal symptoms
  - However, the rate of onset, duration, and severity of the withdrawal symptoms have variation depending on half-life

Conclusions

- Benzodiazepines act as positive allosteric modulators at $GABA_A$ receptors
  - This mechanism of action is shared across the benzodiazepine class
  - Consistent with this shared mechanism of action, the pharmacologic properties of benzodiazepines overlap substantially
  - Overall, from a pharmacological perspective, the benzodiazepines appear to be pharmacologically similar with few differences, including differences in abuse liability
- However, the following presentation of epidemiological data suggests the widespread nonmedical use of alprazolam contributes substantially to the overall abuse liability of the benzodiazepine class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Jana McAninch

U.S. Food and Drug Administration

Epidemiologic Data on Benzodiazepine Use, Misuse, Abuse, Addiction, Overdose, Dependence, and Withdrawal

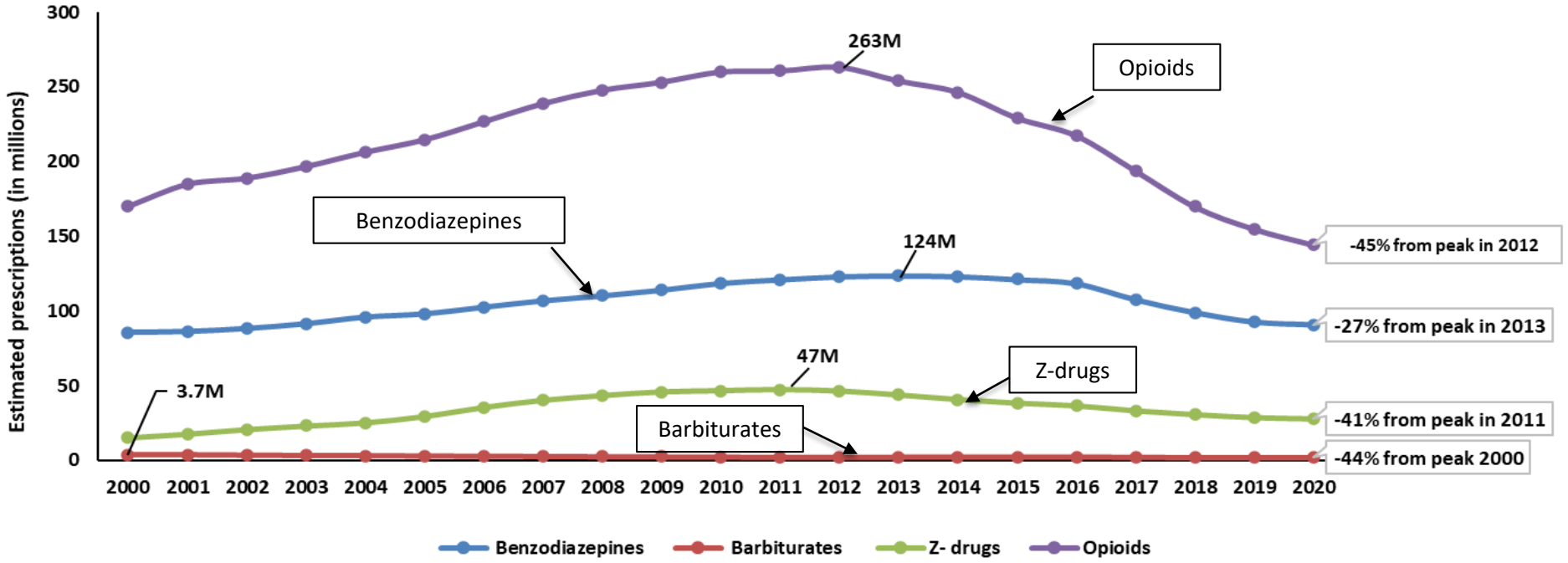
Jana McAninch, MD, MPH, MS
Office of Surveillance and Epidemiology
Division of Epidemiology II
CDER, FDA

Duke-Margolis Meeting
July 12, 2021

Prescription Dispensing Data

U.S. Benzodiazepine Prescribing Trends, in Context

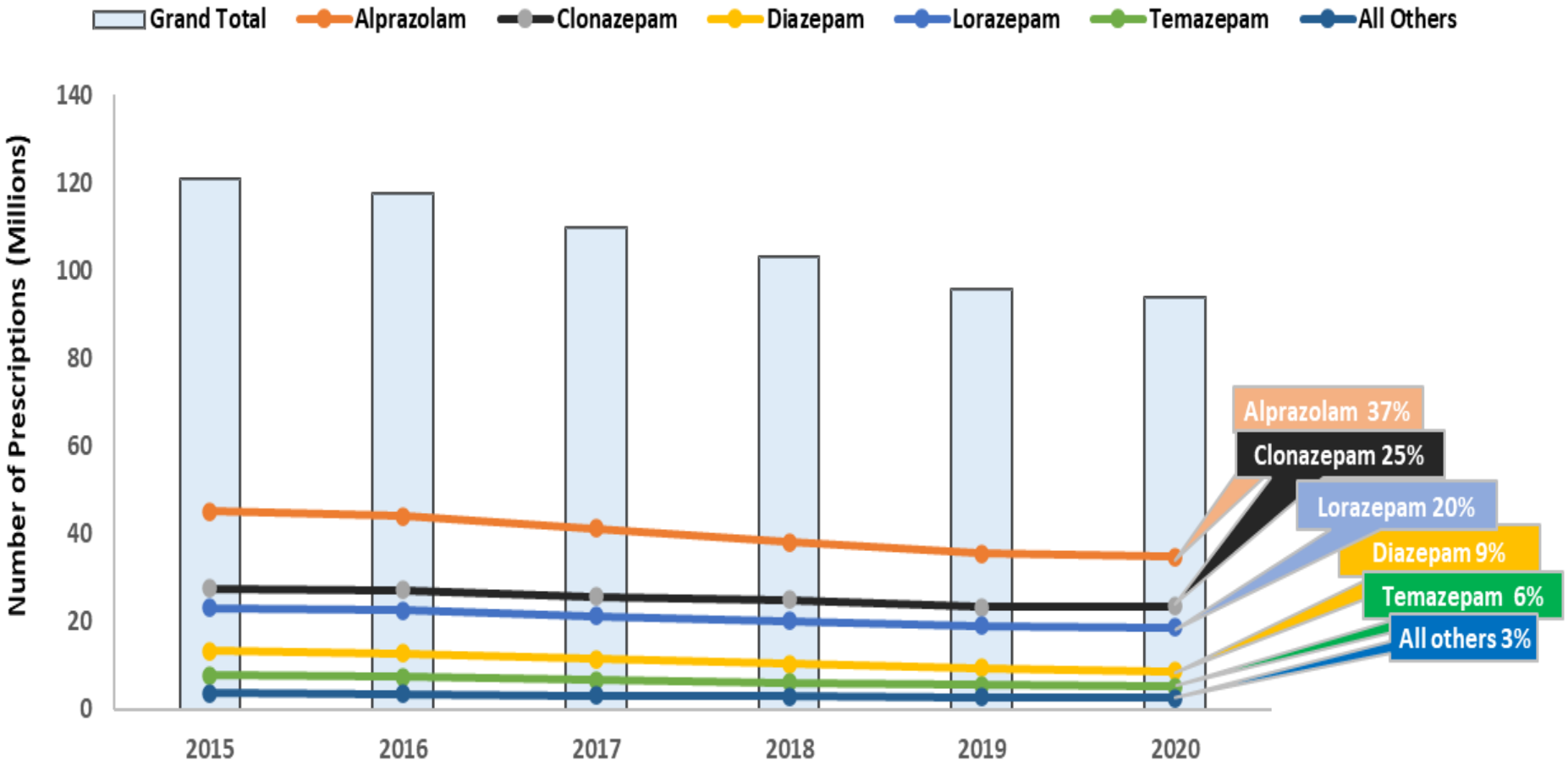
Estimated prescriptions dispensed for Benzodiazepines, Barbiturates, Z- drugs and opioid analgesics (excluding injectables) from U.S. outpatient* pharmacies



Source: IQVIA, National Prescription Audit (NPA). January 2000 - December 2020. Data Extracted June 2021.
*Data includes outpatient retail and mail-order pharmacies. Excludes injectables.
**Opioid analgesics included all non-injectable formulations and excluded cough/cold products and buprenorphine-containing medications for opioid use disorder (MOUD) products
***There was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided and/or reversed starting in 2017. Benzodiazepine estimates using this new methodology were approximately 3% lower compared to legacy estimates. Changes in the projection methodology do not affect prescription volumes dispensed from the mail-order/specialty pharmacies. Retail channel comprised 84% and mail channel 3% of total market, non-retail was not included in this analysis.

Prescriptions Dispensed for Individual Benzodiazepines

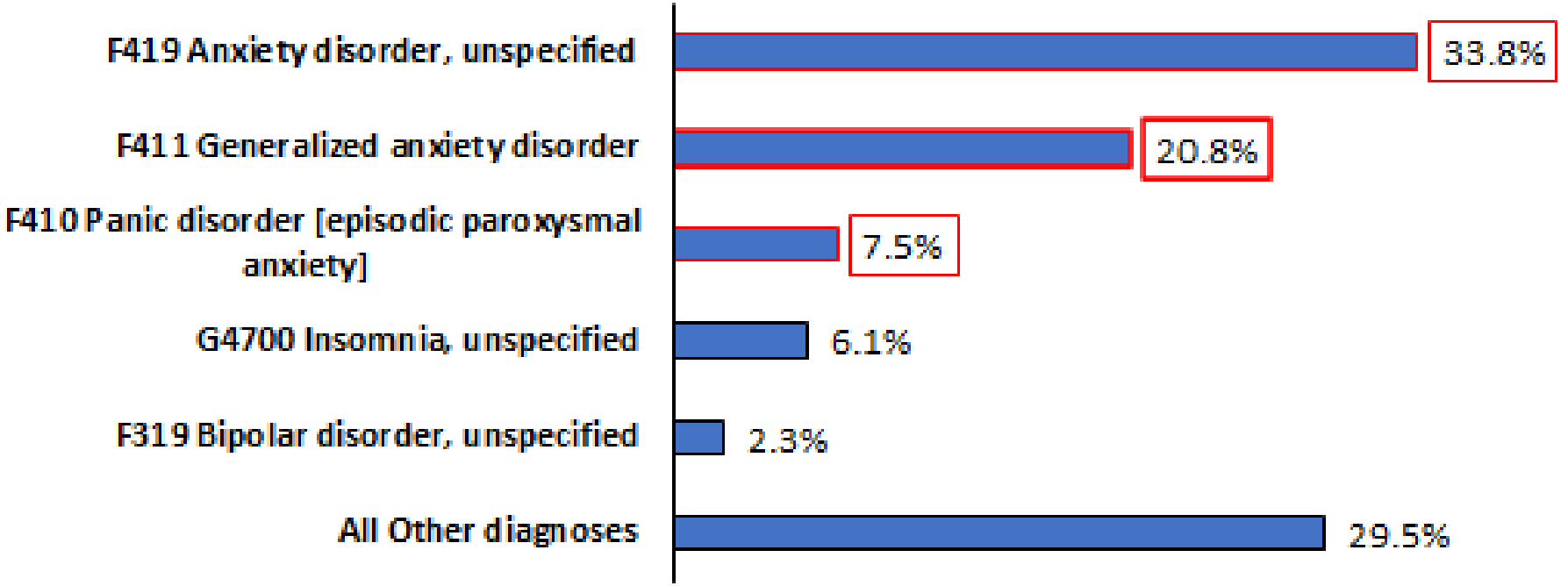
Estimated benzodiazepine prescriptions dispensed from US outpatient pharmacies annually, 2015-2020



Source: Symphony Health™. 2015-2020. Extracted June 2021.
*Other Benzos include clobazam, chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, triazolam, and quazepam

Diagnoses Associated with Benzodiazepine Prescribing

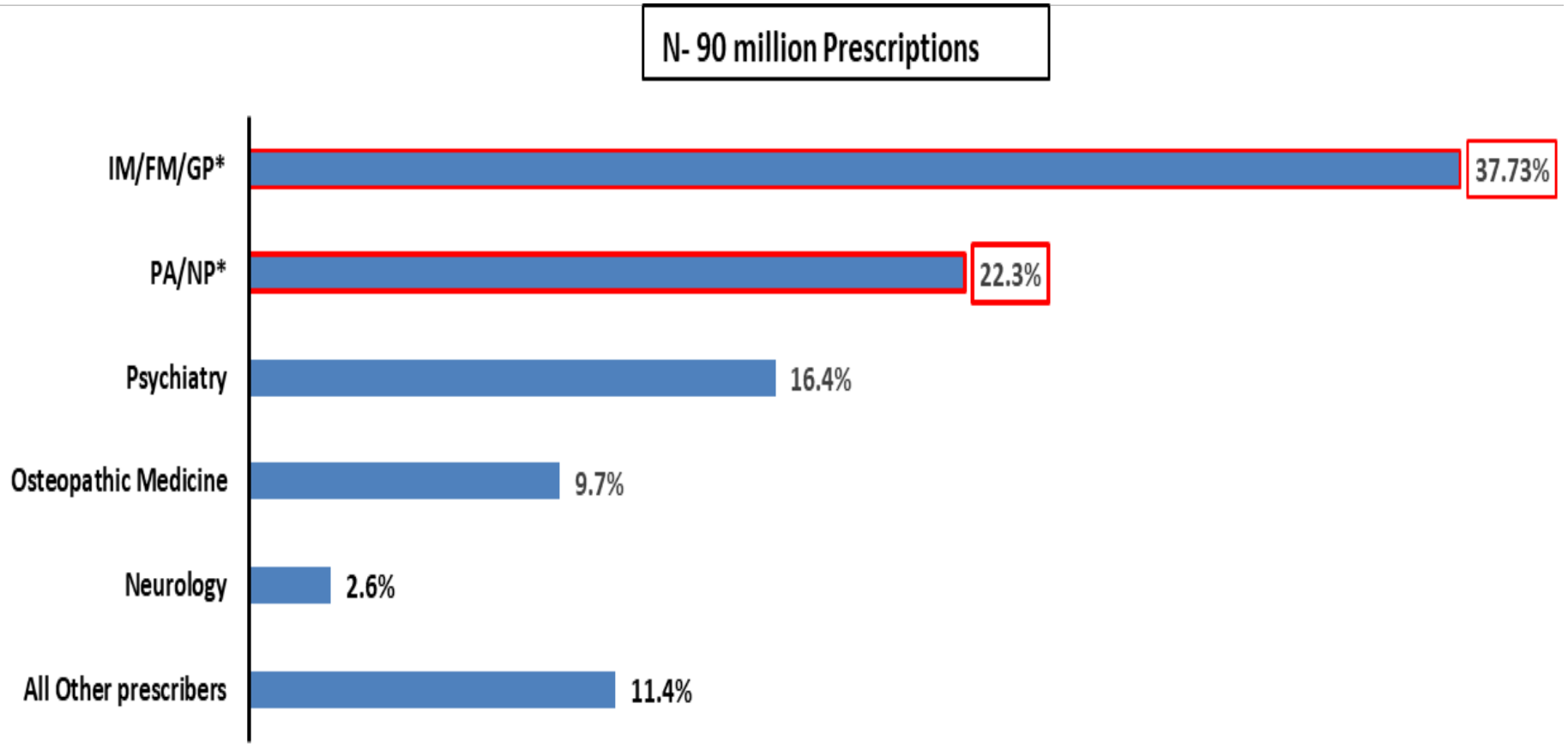
Top groups of diagnoses (ICD-10) associated with the mentions of top 5 benzodiazepines* as reported by



Source: Syneo.TreatmentAnswers™ with Pain Panel. 2021. Data extracted June 2021
**Top 5 Benzodiazepines: Alprazolam, Clonazepam, Lorazepam, Diazepam, Temazepam*

Prescriber Specialty

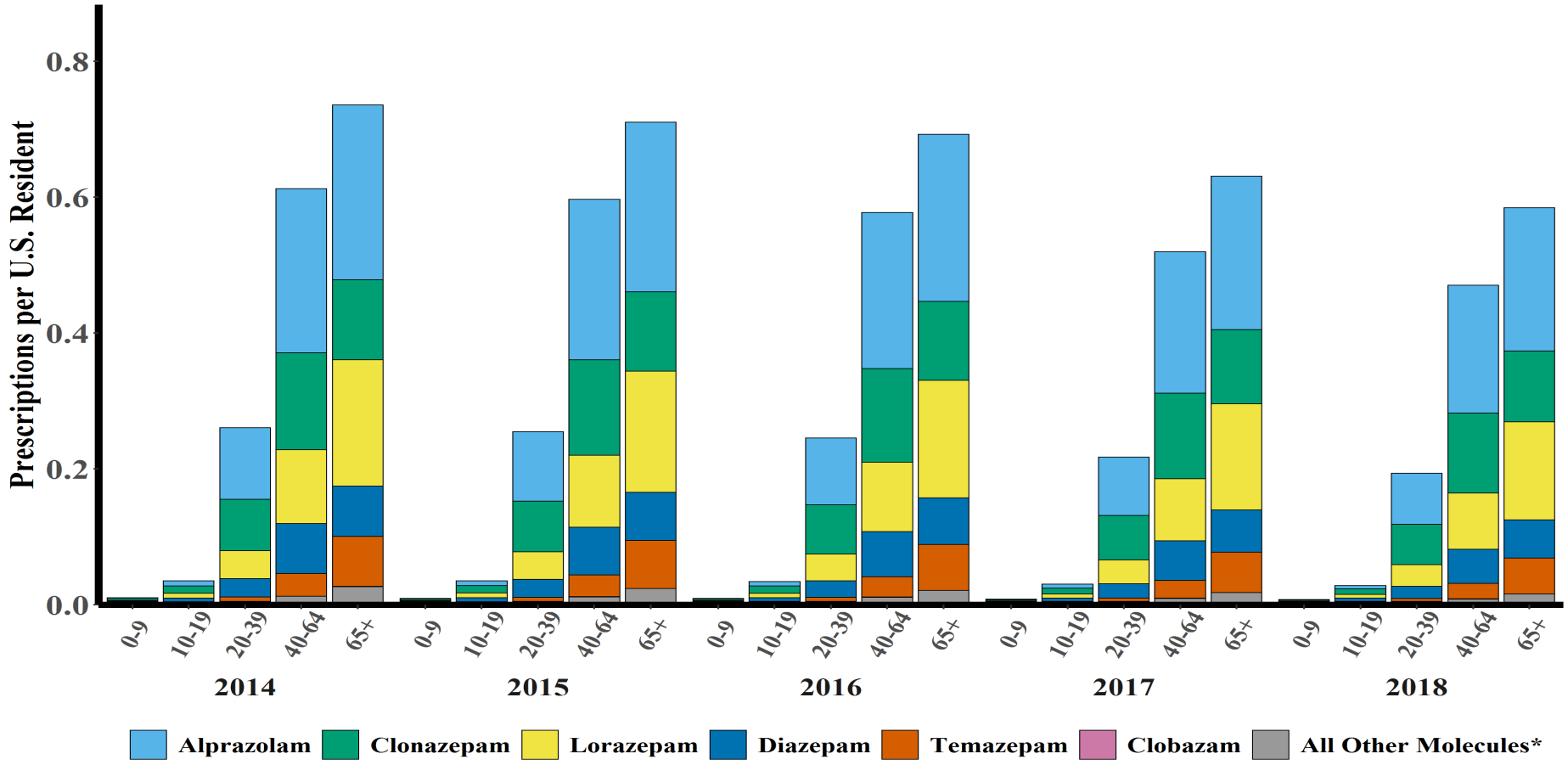
Estimates of outpatient retail prescriptions dispensed for benzodiazepines by top five prescriber specialties in 2020



IM: Internal Medicine, FP: Family Medicine, GP: General Practitioner, PA: Physician Assistant, NP: Nurse Practitioner
Source: IQVIA National Prescription Audit™ (NPA). – Year 2020. Extracted June 2021

Benzodiazepine Prescribing, by Patient Age Group

Benzodiazepine prescriptions dispensed from outpatient retail pharmacies per U.S. resident, by patient age group

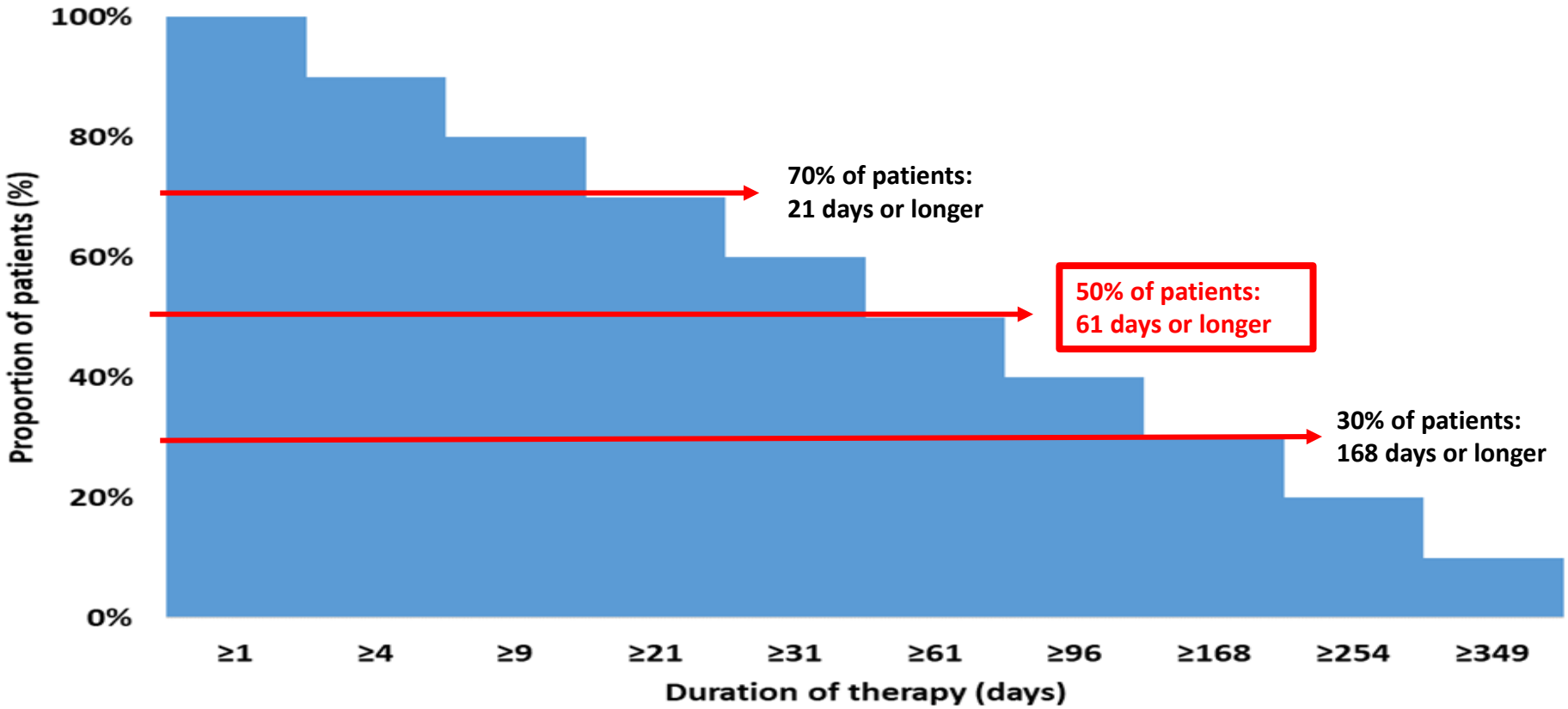


December 2019.File: 2019-800 Benzo PI TRx 1-27-2019.csv. NVSS Census Files. (2019). U.S. Census Populations With Bridged Race Categories. Retrieved from https://www.cdc.gov/nchs/nvss/bridged_race.htm. *All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam

Source: IQVIA, National Prescription Audit™ New To Brand (NPA NTB). January 2014 - December 2018. Data Extracted

Duration of Benzodiazepine Therapy

Nationally estimated proportion of patients with benzodiazepine therapy, stratified by duration of therapy, dispensed from U.S. outpatient retail pharmacies, 2020.

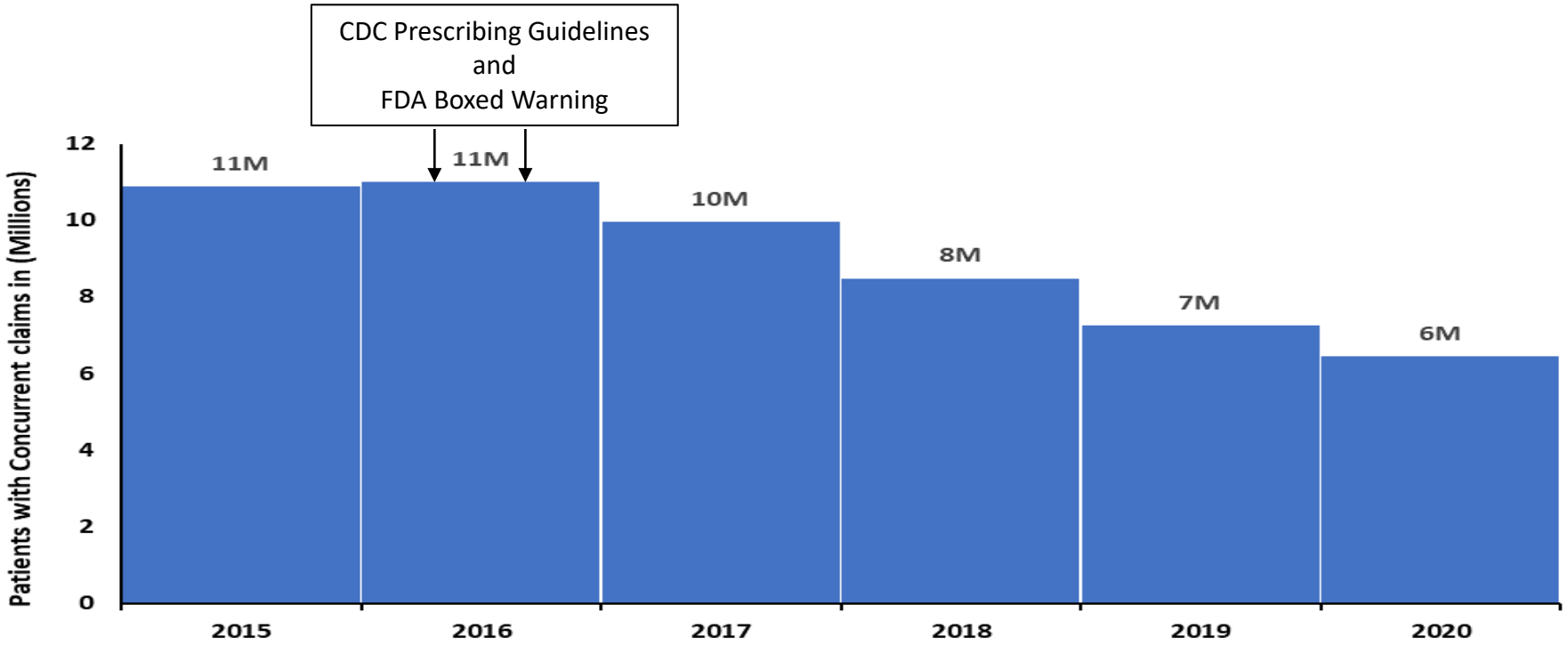


- Duration of therapy increased with age

Source: Symphony Health IDV™ (Integrated Dataverse). Data year 2020. Data extracted June 2021.

Concurrent Dispensing of Benzodiazepines and Opioid Analgesics

Estimated number of patients with concurrent prescriptions for opioid analgesics and oral benzodiazepines from U.S. outpatient retail pharmacies

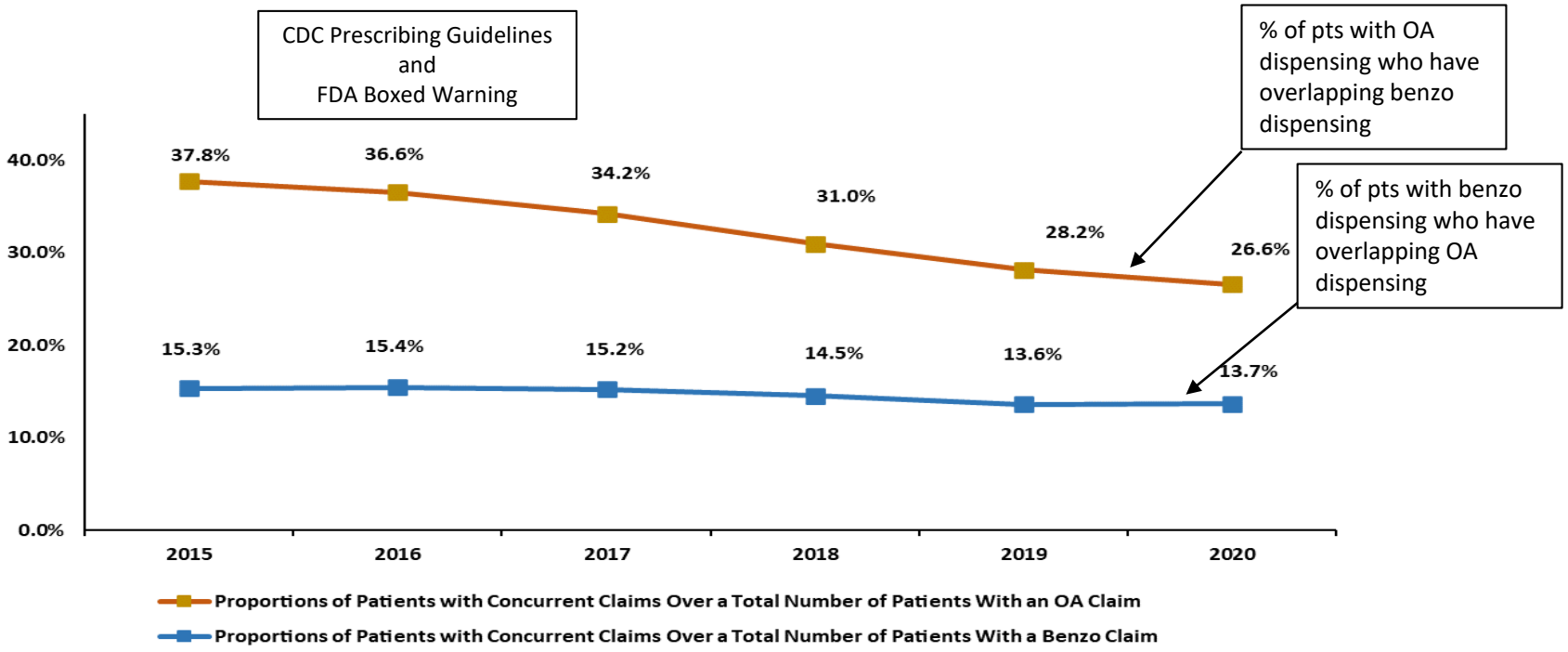


Opioid analgesics included oral, transdermal, and transmucosal formulations and excluded cough/cold products, migraine products, and buprenorphine-containing medications for opioid use disorder (MOUD). Based on dispensed prescription data, estimated number of patients captured with an episode of concurrency defined as an overlap of at least 1 day supply of an opioid analgesic prescription and an oral benzodiazepine prescription.

Source: Symphony Health Solutions' IDV® (Integrated Dataverse). Data extracted June 2021.

Proportions of Patients with Concurrent Dispensing

Proportions of patients with overlapping prescriptions for opioid analgesics and oral benzodiazepines, from U.S. outpatient retail pharmacies

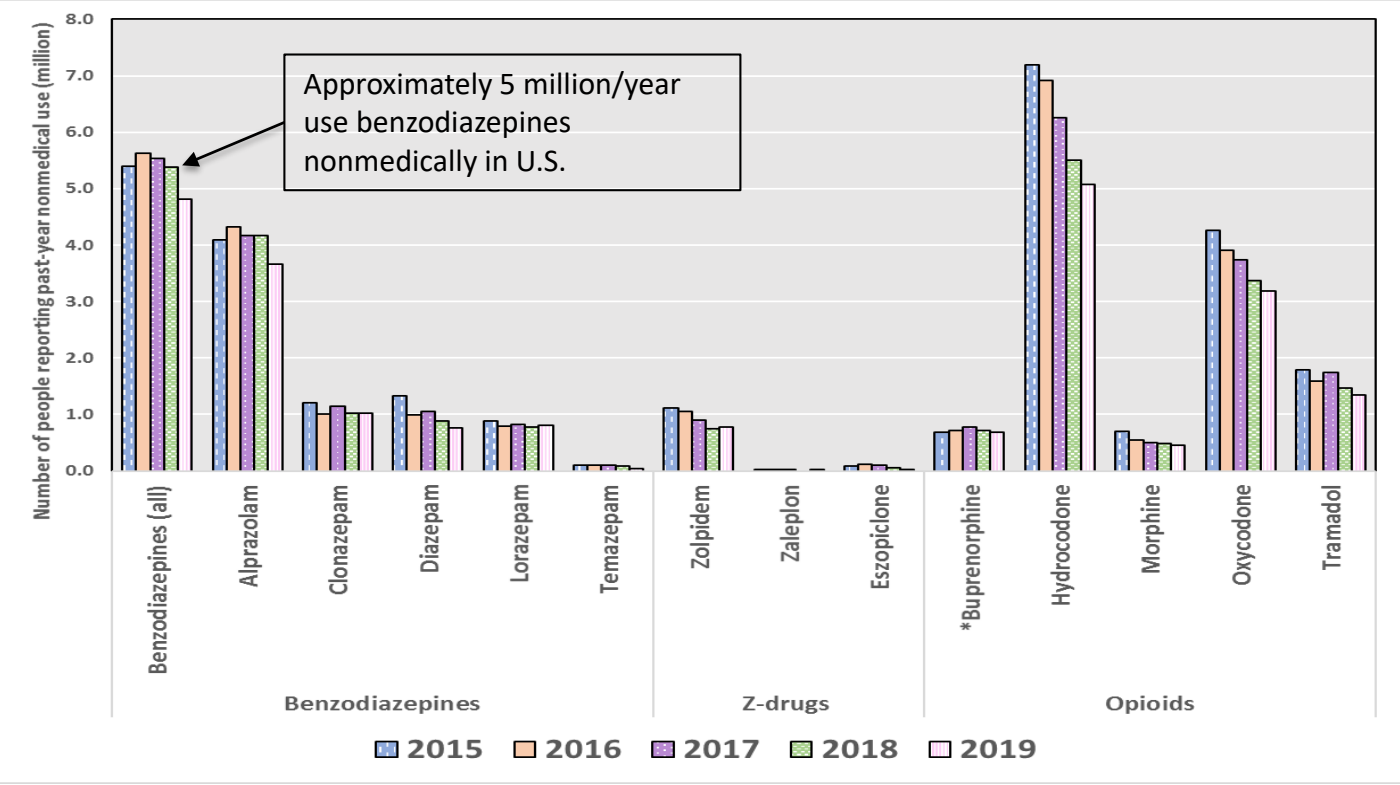


Opioid analgesics included oral, transdermal, and transmucosal formulations and excluded cough/cold products, migraine products, and buprenorphine-containing medications for opioid use disorder (MOUD). Based on dispensed prescription data, estimated number of patients captured with an episode of concurrency defined as an overlap of at least 1 days supply of an opioid analgesic prescription and an oral benzodiazepine prescription.
Source: Symphony Health Solutions' IDV® (Integrated Dataverse). Data years 2017 - 2020. Data extracted June 2021.

Benzodiazepine Nonmedical Use (i.e., Misuse and Abuse) and Associated Morbidity and Mortality

Self-reported Nonmedical Use (NMU)

Estimated Number of People Aged 12+ years with Past-Year Nonmedical Use,*
National Survey on Drug Use and Health (NSDUH)



Highest prevalence of benzodiazepine NMU was in 18–25 year-olds.

Sources for benzodiazepine NMU:

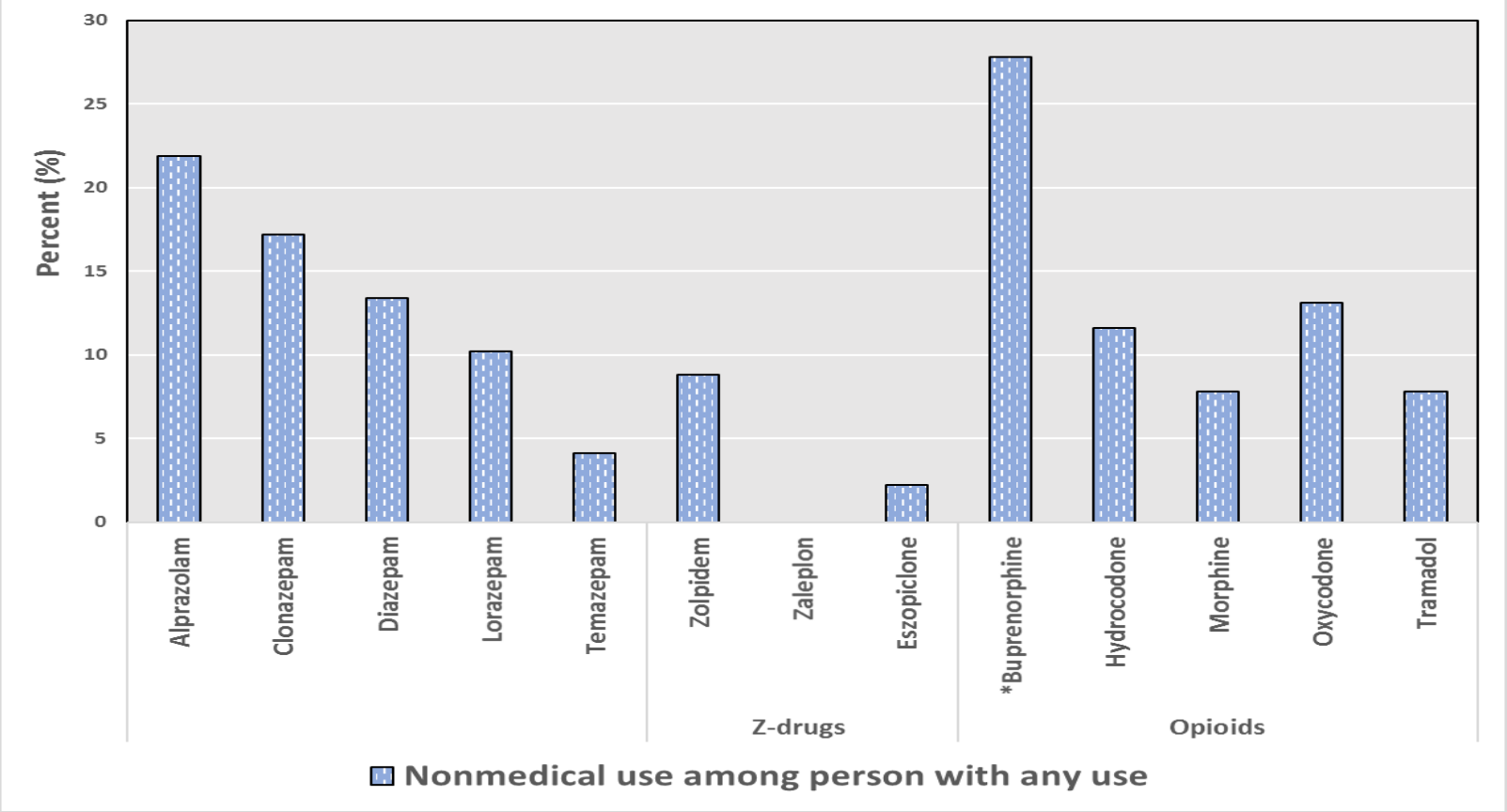
- 53% got free from friend or relative
- 20% got from one doctor
- 12% bought from friend or relative

*Nonmedical use = any use other than as directed, for therapeutic or non-therapeutic reasons (NSDUH uses the term “misuse”)

*buprenorphine includes both analgesic products and those indicated for OUD treatment

Nonmedical Use Among Those with Any Use

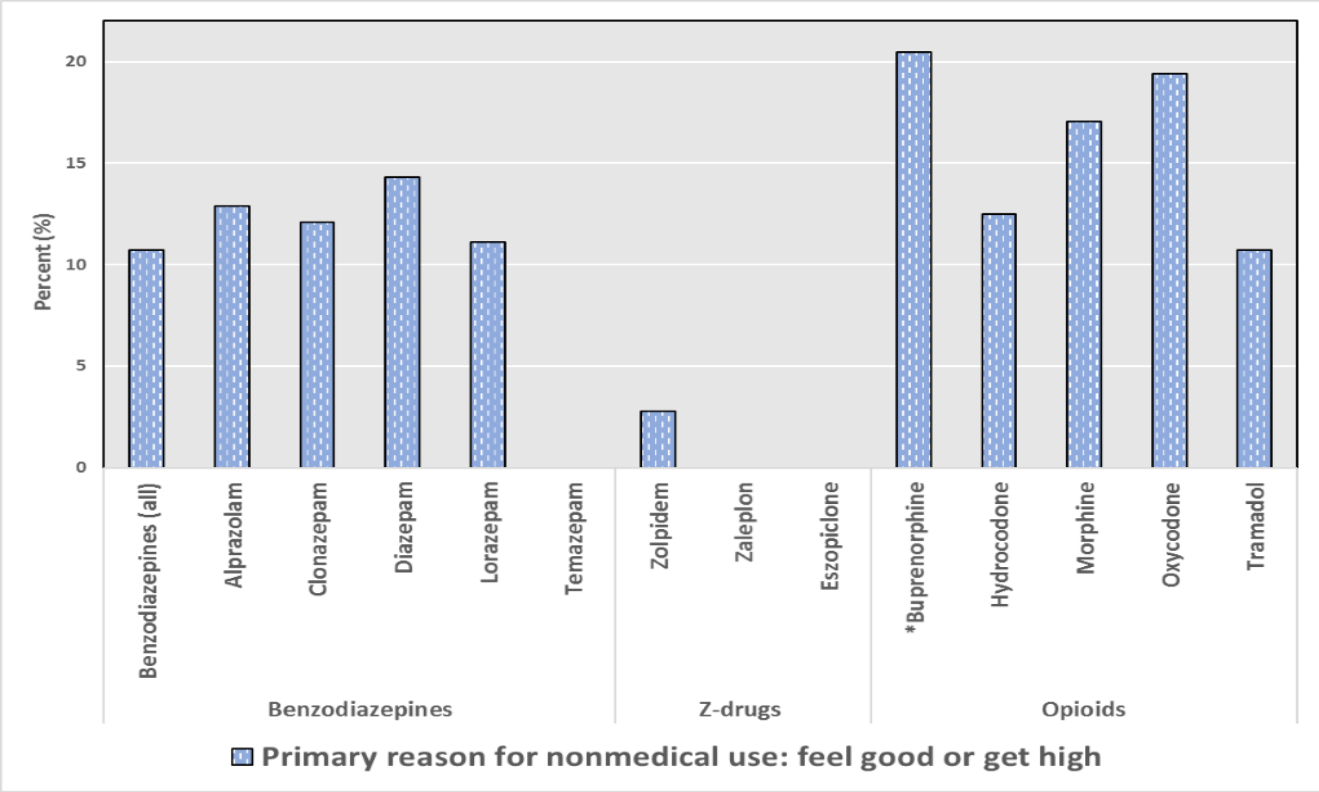
Among those reporting <u>any</u> past-year use of a drug, the percent reporting using it nonmedically, NSDUH 2019



*buprenorphine includes both analgesic products and those indicated for OUD treatment

Reasons for Nonmedical Use

Percent reporting primary reason for nonmedical use of the drug was **"to feel good or get high,"** NSDUH 2019



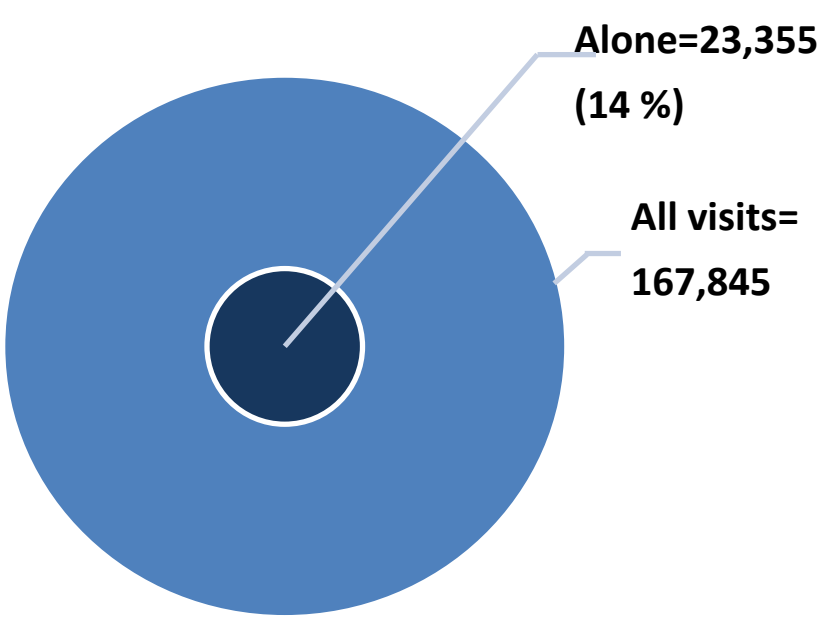
Most common reasons for benzodiazepine nonmedical use were:

- to relax or relieve tension
- to help with sleep
- help with feelings or emotion

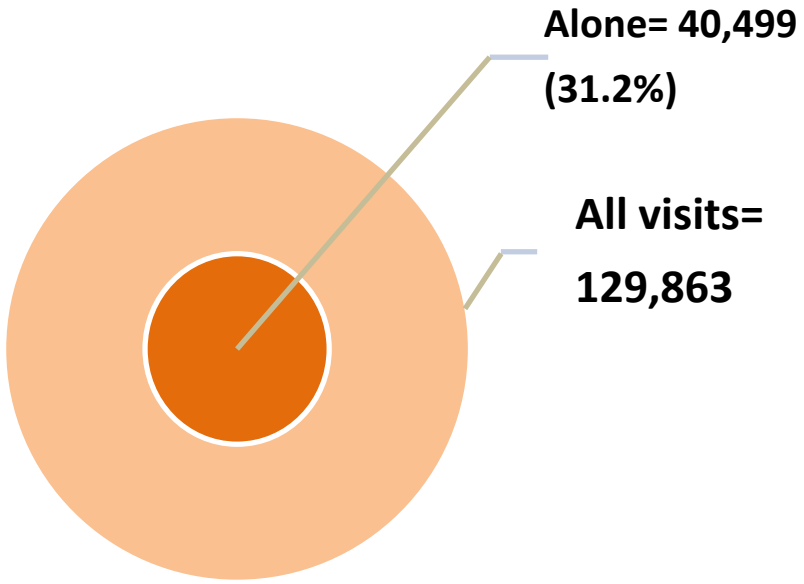
*buprenorphine includes both analgesic products and those indicated for OUD treatment
Note: Data were not available for temazepam, zaleplon, and eszopiclone.

Emergency Department Visits Due to Nonmedical Use:*
Overall and Alone (Single-substance)

Benzodiazepines



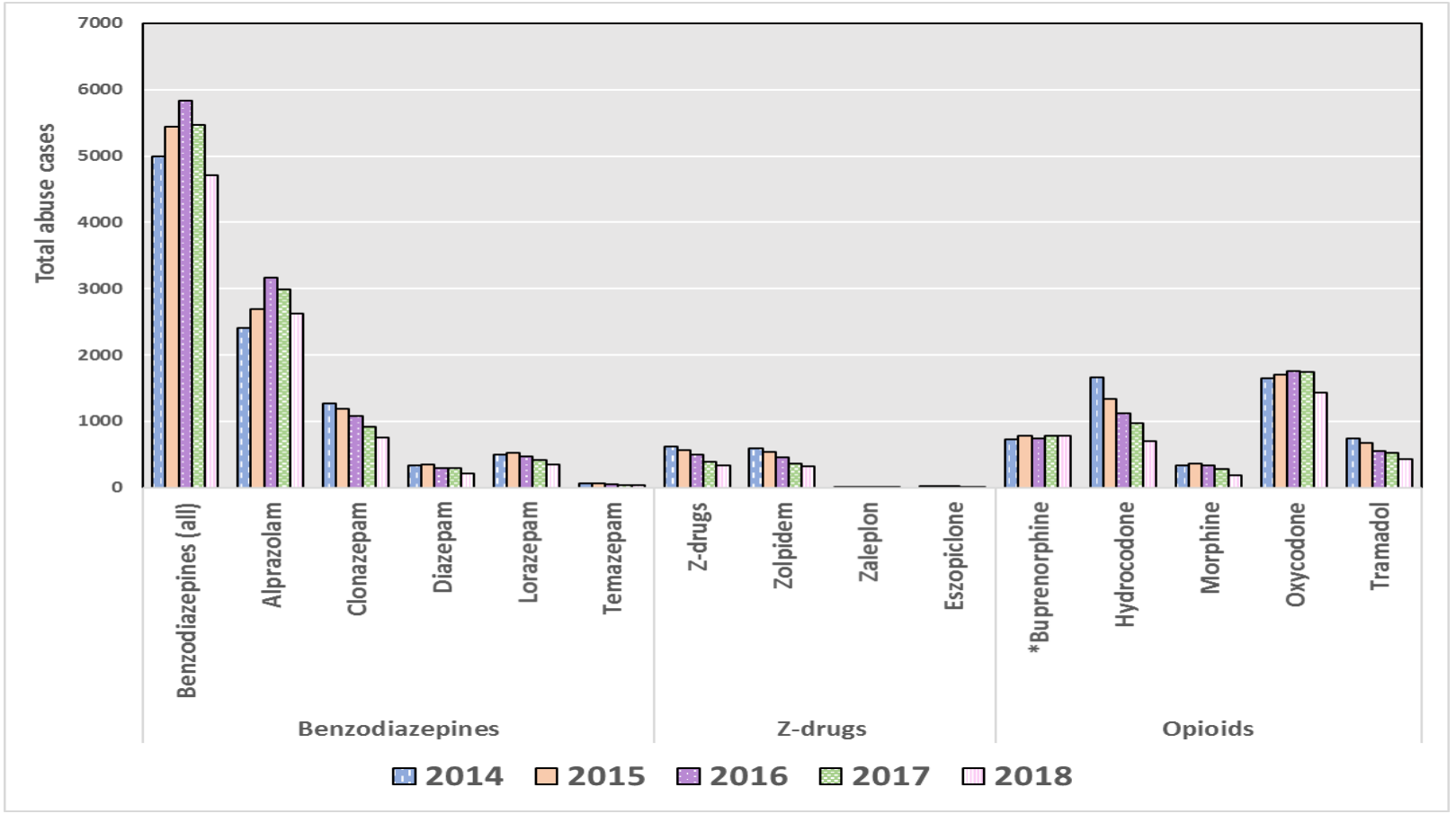
Rx opioids



- Half of benzodiazepine nonmedical use visits were in patients <35 years old

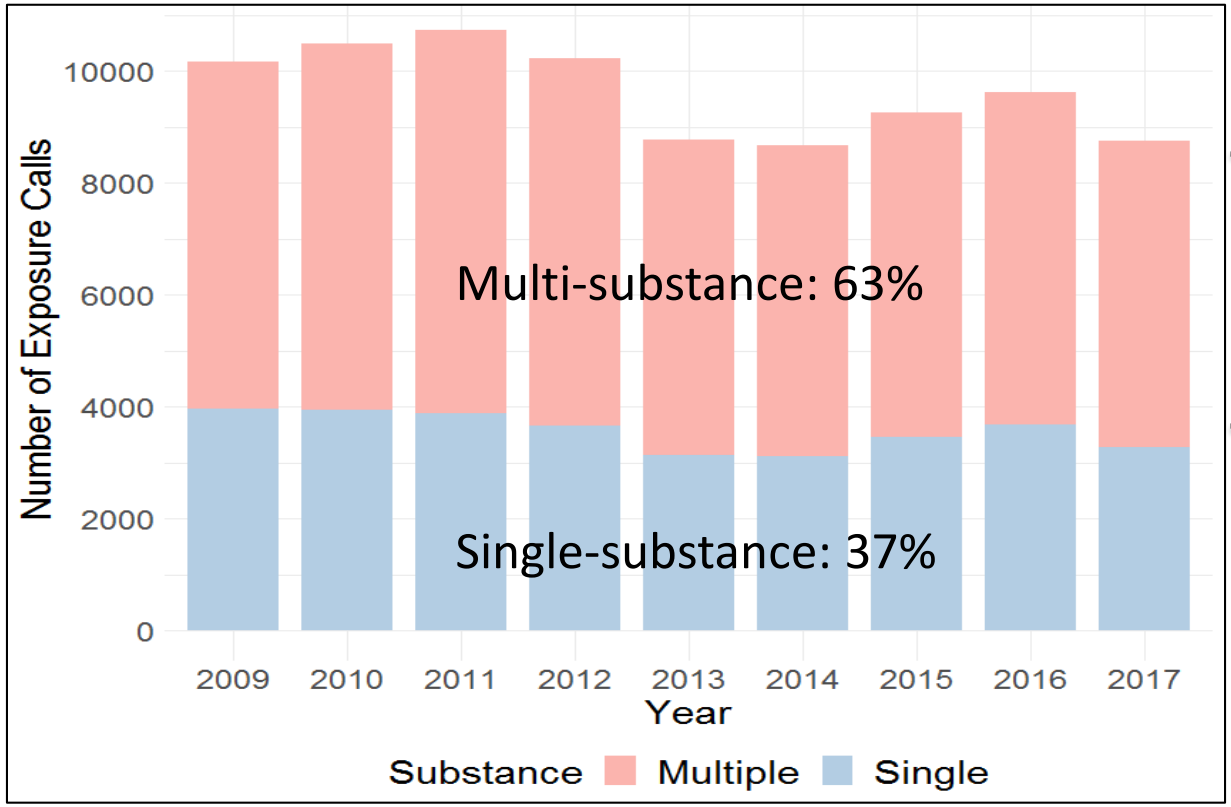
*Nonmedical use case = abuse, therapeutic misuse, or overdose with unknown intent
Source: Geller AI*, Am J Prev Med* 2019, analysis of 2016 National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES)

Abuse Cases, U.S. Poison Center Exposure Calls



*buprenorphine was not considered a formal epidemiologic comparator
Source: FDA analysis of National Poison Data System

Benzodiazepine Misuse and Abuse Cases, U.S. Poison Center Calls



Most common co-involved substances with benzodiazepines:

- Rx opioids
- Alcohol
- Stimulants

Medical outcomes more severe than single-substance calls

www.fda.gov

Source: FDA analysis of National Poison Data System (NPDS)

Addiction—
Drugs of Abuse Reported in SUD Treatment Admissions

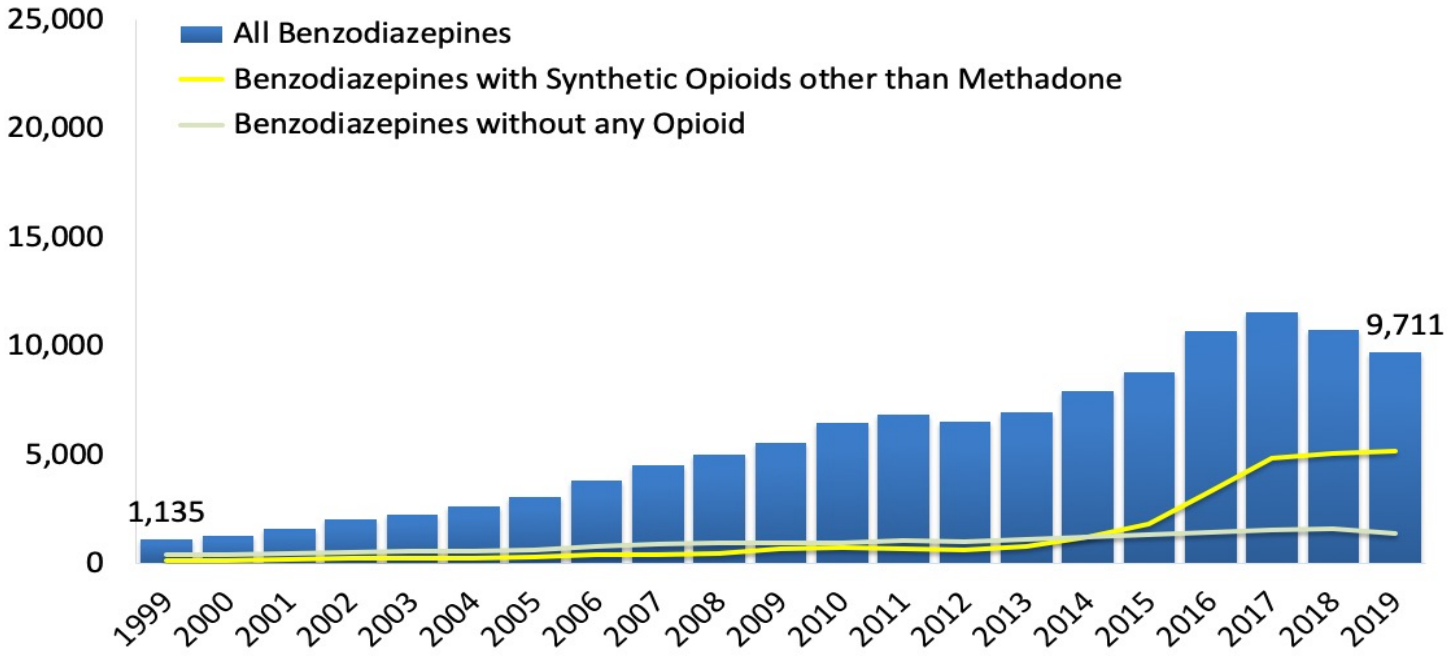
Treatment Episode Data Set (TEDS), 2018

	Total (N=1,587,849)	Primary Drug	Secondary Drug	Tertiary Drug
Benzodiazepines	**60,562**	**10,790**	31,297	**18,475**
Alprazolam	34,399	6,243	18,028	10,128
Clonazepam	1,571	308	785	478
Diazepam	4,300	625	2,267	1,408
Lorazepam	393	82	202	109
Other	19,899	3,532	10,015	6,352
Prescription opioids[†]	**47,771**	**30,137**	12,992	**4,642**
Buprenorphine*	7,808	3,197	2,858	1,753
Hydrocodone	5,447	3,043	1,648	756
Oxycodone	33,810	21,055	9,491	3,264
Tramadol	362	207	109	46

[†] Includes codeine, hydrocodone, hydromorphone, meperidine, oxycodone, pentazocine, propoxyphene, and tramadol
*buprenorphine includes both analgesic products and those indicated for OUD treatment

Benzodiazepine Involvement in Overdose Deaths

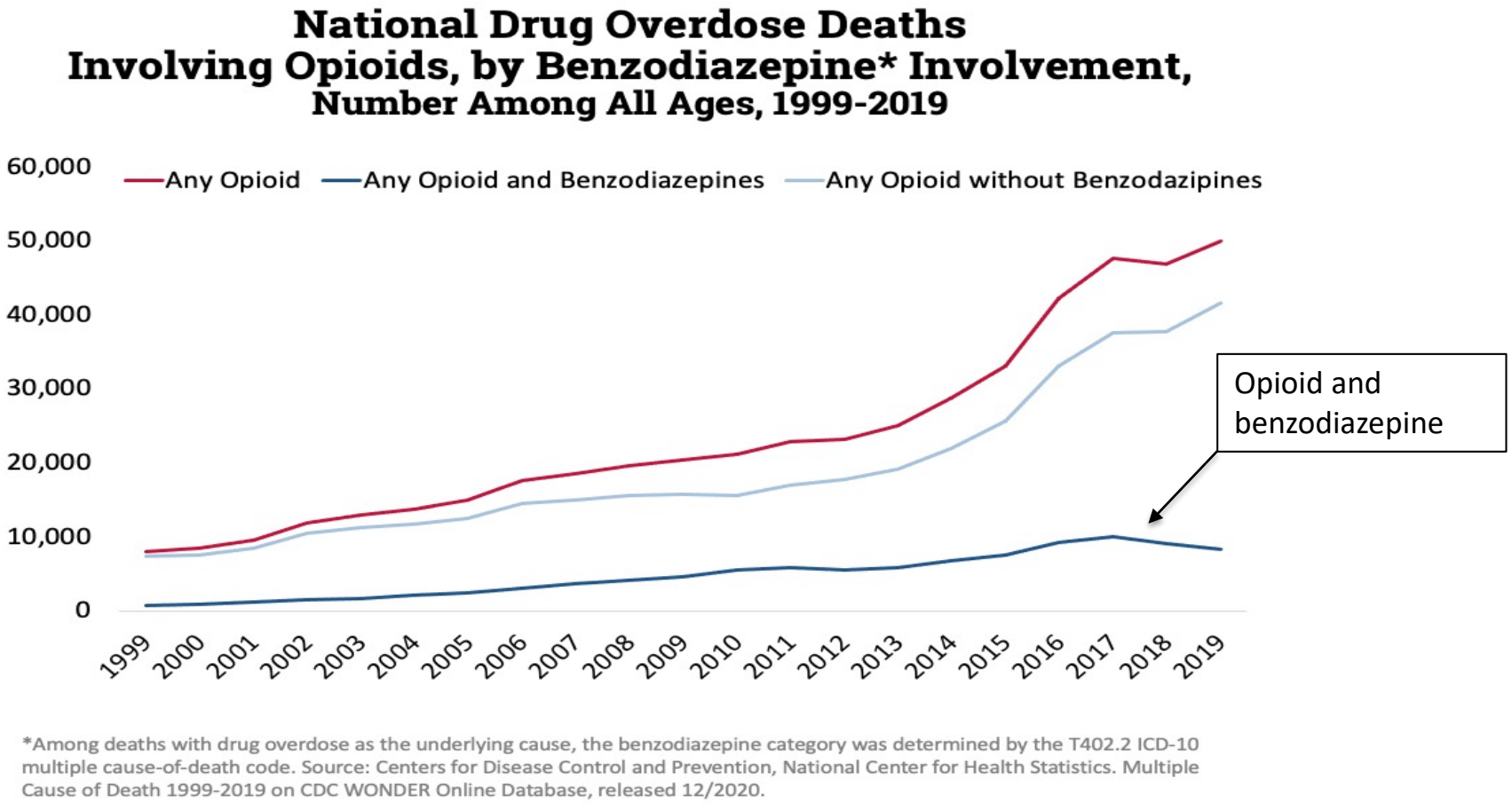
Figure 8. National Drug Overdose Deaths Involving Benzodiazepines*, by Opioid Involvement, Number Among All Ages, 1999-2019



*Among deaths with drug overdose as the underlying cause, the benzodiazepine category was determined by the T402.2 ICD-10 multiple cause-of-death code. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released 12/2020.

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

Benzodiazepine Co-Involvement in Opioid-Involved Overdose Deaths



https://www.drugabuse.gov/drug-topics/opioids/benzodiazepines-opioids

Comparing Rates Across Drugs—
Adjusting for Prescribed Availability

- Of the benzodiazepines, alprazolam had the highest frequency for all measures of nonmedical use, abuse, and related harms
- Alprazolam also has the highest prescription dispensing rates
- After adjusting for differences in prescription volume, alprazolam still had the highest rates for ***some*** outcomes…
  - Abuse-related ED visits
  - Poison center abuse cases

  but ***not*** others (diazepam was similar or higher)
  - Self-reported nonmedical use
  - Overdose* death involvement

*unintentional or undetermined intent

Counterfeit and Unapproved/"Designer" Benzodiazepines—
A growing concern, but little data

AP

Law officers warn of potentially lethal drug sold as Xanax

February 11, 2021

"Alert: Counterfeit Street Pills and Fentanyl-Related Overdoses in Carroll County

… counterfeit Xanax pills, sold for as little as $5 on the street, include a deadly combination of Xanax and fentanyl."

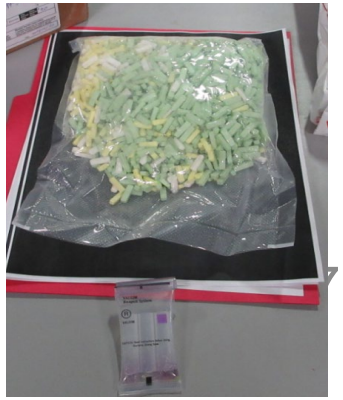
"The 'designer' benzodiazepines often come in pills that imitate Xanax (alprazolam) pills. Some have the same color and appearance as Xanax and others are yellow or green bar-type pills, all containing such unapproved substances as **flualprazolam** and **clonazolam**, according to case reports from the King County Medical Examiner's Office."

Background: Novel psychoactive substances, such as designer benzodiazepines unapproved for therapeutic purposes, are an emerging concern worldwide. They have unknown or unpredictable pharmacological properties. Using a case example, we discuss the use of "Xanax bars," which now generally do not contain the pharmaceutical alprazolam. We describe the difficulty in detecting these substances and the development of a use disorder including adverse outcomes such as seizures when stopped. The evidence for management is anecdotal.

Houck et al., 2021

"Deadly drug flualprazolam found in fake Xanax tablets"

Oct 12 2020



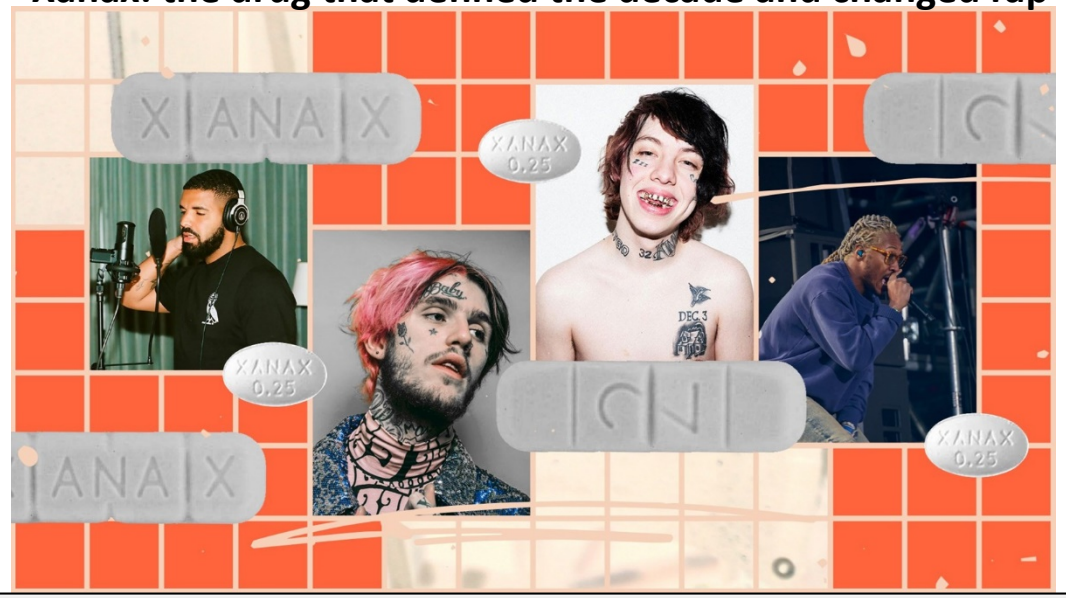
"CBP Seizes Over 35 Pounds of Counterfeit Xanax"

May 1, 2020

Cultural Influences on Drug Choices

"Generation of drugs: A look inside the Xanax and lean culture in hip-hop"

"Xanax: the drug that defined the decade and changed rap"



"Bars: The Addictive Relationship With Xanax & Hip Hop"

"'**Xanny'** is a song by American singer Billie Eilish from her debut studio album"

Dependence and Withdrawal

Epidemiologic Data on Dependence and Withdrawal

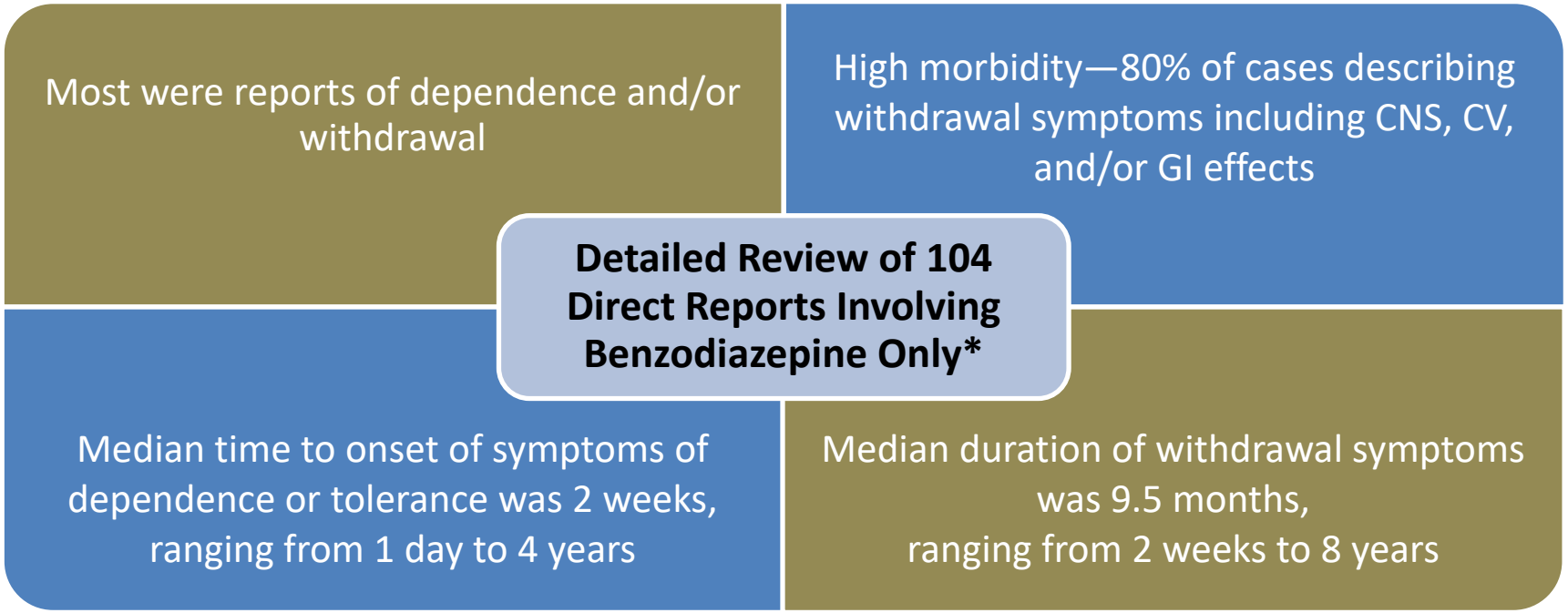
- Poison center calls for benzodiazepine withdrawal* increased 60% from 2009 to 2017 (from 158 to 253)
- Cohort studies[1-4] suggest risk factors for long-term and/or high-dose benzodiazepine may use include:
  - Alcohol dependence[1]
  - Depression, anti-depressant medication use[1,2,3,5]
  - Older age[2,3]
  - Female sex[2,3,4]
  - Lower education and income levels[2,4]

*single-substance exposure cases

1. Manthey L. *Addiction* 2012
2. Airagnes G. *BMC Public Health* 2019
3. Juijendijk HJ. *British J Clin Pharm* 2008
4. de las Cuevas C. *Psychopharmacology* 2003
5. Mol AJ. *Comprehensive Psychiatry 2005*

FDA Adverse Events Reporting System (FAERS) Analysis

- 40,000+ reports* of drug abuse, dependence, or withdrawal (through June 30, 2019)



***Because many factors can influence whether a case is reported, these numbers do not represent incidence or a representative sample of events or support direct comparison across benzodiazepines**

Notes on FAERS Dependence and Withdrawal Cases

- Multiple cases where patient was instructed “to quit cold turkey” when experiencing benzodiazepine withdrawal symptoms
- Descriptions of symptoms of long duration were generally consistent with medical literature describing *protracted withdrawal*,[1] although often difficult to distinguish from re-emergence of underlying symptoms
- Some reports from healthcare providers and patients explicitly requested stronger warnings and better education about the risk of dependence and withdrawal, even at lower therapeutic doses and with short periods of use.

1. Ashton, H. Protracted Withdrawal Syndromes from Benzodiazepines, *J Subst Abuse Treatment* 1991

Summary

Prescribing Patterns

- Benzodiazepines are widely prescribed, although prescribing has been trending down
- Most of the prescribing is by primary care providers.
- Anxiety disorders are most common associated diagnoses
- Long-term use is common
- Highest prescription rates are in older adults
- Co-prescribing of benzodiazepines with opioid analgesics has declined since 2016 but remains common

Nonmedical Use, Addiction, Overdose

- Nonmedical use of benzodiazepines is a significant public health problem, contributing to substantial morbidity and mortality
  - Highest rates in older teens, young adults
  - Most nonmedical use is for therapeutic reasons
  - Most harms occur in context of polysubstance use
- Alprazolam has highest frequencies of nonmedical use and harms—high prescribing rates, counterfeits, cultural influences are likely contributors
- Good estimates of addiction risk are lacking
  - Commonly reported drug at treatment admission but usually not primary
- Most recent trends appear stable or possibly declining
  - Benzodiazepine involvement in opioid overdoses is decreasing
  - 2020??—data lags
  - But, growing role of counterfeit/unapproved benzos?

Dependence and Withdrawal

- Epidemiologic data are limited, but suggest withdrawal cases may be increasing
- FAERS reports describe serious withdrawal symptoms, with onset as early as days to weeks, and with some symptoms lasting months
- Some reports suggest lack of appropriate measures to prevent and manage withdrawal symptoms

Benzodiazepine Boxed Warning

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death**. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation [see Warnings and Precautions (5.1), Drug Interactions (7.1)].

- The use of benzodiazepines, including [DRUG], exposes users to **risks of abuse, misuse, and addiction**, **which can lead to overdose or death**. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing [DRUG] and throughout treatment, assess each patient's risk for abuse, misuse, and addiction [see Warnings and Precautions (5.2)].

- The continued use of benzodiazepines, including [DRUG] , may lead to clinically significant **physical dependence**. The risks of dependence and **withdrawal** increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of [DRUG] after continued use may precipitate acute withdrawal reactions, which can be life-threatening. **To reduce the risk of withdrawal reactions, use a gradual taper** to discontinue [DRUG] or reduce the dosage [see Dosage and Administration (2.2), Warnings and Precautions (5.3)].


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Kurt Kroenke

Indiana University School of Medicine

Balancing the Risks and Benefits of Benzodiazepines

Kurt Kroenke, MD, MACP
Chancellor's Professor of Medicine
Indiana University School of Medicine
Regenstrief Institute, Inc.

What we likely agree on

- Benzodiazepines are greatly overused
- Benzos are associated with dependency and other harms
- Co-administration with other substances (alcohol, opioids, etc.) substantially increases risk
- Benzos have some clinical value (e.g, seizure disorders, short-term for acute anxiety, alcohol withdrawal, preop)
- Safer treatments are available for chronic anxiety (SSRIs/SNRIs, psychotherapy) and insomnia (CBT)

Sources -- Systematic Reviews

- Search terms: benzodiazepine AND systematic review or meta-analysis
- Focus: benefits & risks in clinical samples (not basic or translational science studies)
- Search period: 2010-2021
- Data source: PubMed, Google Scholar
- 43 reviews and/or meta-analyses retrieved
  - *25 full articles, 18 additional abstracts*

Burden of Anxiety

- Prevalence: 13% in population; 20% in primary care [1]
- Anxiety → 1.5 million years lived with disability (YLD) in the US [2]
- 5th leading cause of YLD (of top 30 diseases)
- Most common mental disorder in elderly (20%) → impairment & ↑ health costs[3]

1) Kroenke, Ann Intern Med 2007; 2) Murray, JAMA 2013
3) Hohls, J Affective Disorder 2018

Efficacy of Benzodiazepines for Anxiety

- Benzodiazepines more effective than placebo in generalized anxiety disorder (meta-analysis of 58 trials; > 5400 participants) [1]
- Benzodiazepines more effective than placebo in panic disorder (2 meta-analyses) [2,3]
- Benzos more effective than placebo in elderly.[4]
- Antidepressants (SSRIs/SNRIs) and benzos are generally similar in terms of efficacy [5,6]
- Benzo benefits were greatest in those with higher anxiety and in trials of shorter duration [1]

1) Gale C, J Psychopharmacol 2019; 2) Du Y, Asian J Psychiatry 2021
3) Breilmann, Cochrane 2019; 4) Gupta, Ann Clin Psychiatry 2020
5) Shinfuku, Int Clin Psychopharm 2019; 6) Offidani, Psychother Psychosom 2013

What about Chronic Insomnia?

- Affects 6-10% of adult population [1]
- $30 to 107 billion spent on insomnia and $63 billion lost work productivity in US each year [1]
- Only 2 drug classes are evidence-based (Z-drugs, suvorexant) → short-term (4 wks) small effects [2]
- Inconclusive benefits → benzodiazepines, antidepressants (e.g., trazodone), melatonin [2]
- CBT for insomnia has strongest evidence [1,3]

1) Qaseem, Ann Intern Med 2016; 2) Wilt, Ann Intern Med 2016
3) Brasure, Ann Intern Med 2016

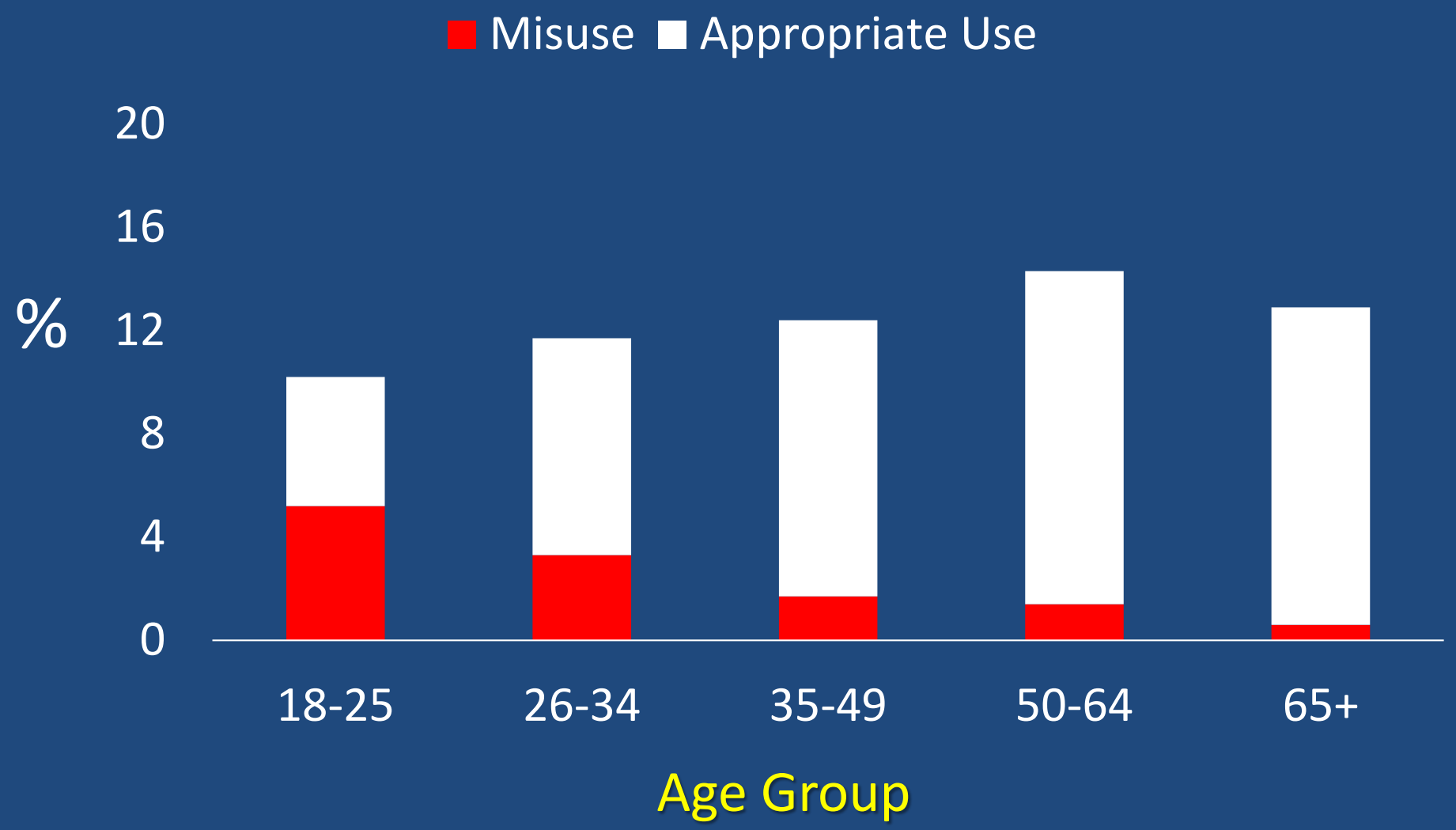
Use and Misuse of Benzodiazepines

- 30 million patients in USA use benzos in past year, with 17% reporting misuse
- Misuse = 1) nonmedical use; or 2) use "in any way a doctor did not prescribe"
- Substance use disorders ↑ benzo misuse
  - Opioid use disorder ↑ benzo misuse 20-fold
  - Alcohol use disorder ↑ benzo misuse 4-fold
- Misuse in 51% of 18-25 y/o vs. 4% if ≥ 65 y/o.

Maust DT, Psychiatric Services 2019; Votaw VR, Drug Alc Dependence 2019

Benzodiazepine Use & Misuse by Age

Maust DT et al, Psychiatric Services 2019;70:97-106



Benzo Prescriptions and Overdose Deaths

	1996	2013
Received prescription	4100 per 100,000	5600 per 100,000
Overdose deaths *Opioids involved in 75% of deaths*	0.58 per 100,000	3.07 per 100,000
Overdose deaths per adults prescribed benzo	1.4 per 10,000	6.6 per 10,000
Prescribed benzo without overdose death	9998 per 10,000	9993 per 10,000

Bachhuber, Am J Pub Health 2016

Benzos & Dementia - Inconclusive

- Meta-analysis of 10 studies (6 case-control; 4 cohort) → BZD use ↑ dementia risk (RR =1.51)[1]
- Second meta-analysis also showed ↑risk (OR=1.39), not explained by reverse causation or psychiatric comorbidity[2]
- In population based Danish cohort of patients with affective disorders (n=171,286)[3]
  - 76% had any use of BZD or z-drug.
  - 4.2% got dementia (median follow-up of 6.1 years)
  - No association of BZD with incident dementia
  - In case-control, slight risk in lowest BZD users (OR = 1.08) but protective effect in highest users (OR = 0.88)

1) He Q et al, J Clin Neurol 2019; 2) Penninkilampi R et al, CNS Drugs 2018;
3) Osler M et al, Am J Psychiatry 2020

Medications with Increased Falls Risk

Medication	OR
SSRI Antidepressants	2.02
Long-acting Benzodiazepines	1.81
Opioids	1.60
Anticonvulsants	1.55
Antipsychotics	1.54
Anti-Parkinson drugs	1.54
Analgesics	1.42
Tricyclic Antidepressants	1.41
Short-acting Benzodiazepines	1.27

Seppala LJ et al. 2018. JAMDA e1-e8, e11-e17

Long-term Benzodiazepine Use

- 41 register-based studies, 1994-2014
- Prevalence of 3% in general population
- About 1 in 3 benzo users are long-term
- More common in older adults
- Usually low stable doses. Dose escalation occurs in only 2-20% of long-term users
- Longer use and higher doses more common for anxiety than insomnia

Kurko TAT, European Psychiatry 2015; Willems IAT, Fam Pract 2013

Tapering or Discontinuing Benzos

- Interventions which have some evidence [1-3]
  - Letters to patients educating/advising about BZD
  - Prescriber educating/advising patient
  - Alerts to clinicians when prescribing BZD
  - Pharmacist to physician detailing on specific patients
  - Patient support groups
- Numerous barriers have been identified [4,5]
- Paucity of evidence-based tapering schedules

1) Smith AJ, BMC Health Serv Res 2010; 2) Mugunthan K, Brit J Gen Pract 2011;
3) Riberio, Fam Pract 2021; 4) Rasmussen, Metabolites 2021;
5) Lynch, Addiction 2020

Learning from the Opioid Backlash

1. Don’t suddenly and unilaterally discontinue in the millions of chronic benzodiazepine users
2. Avoid overly restrictive regulatory policies (especially DEA, state legislatures & boards, etc.)
3. Consider patient’s access and reimbursement for nonpharmacological anxiety treatments
4. Ensure anxiety is adequately treated and controlled if long-term benzos are discontinued

Kroenke & Cheville, JAMA 2017. Kroenke et al. Pain Medicine 2019.
Dowrick et al, N Engl J Med 2019.

Key Clinical Recommendations

- Use less benzos and, when used, prescribe at lowest effective dose and shortest time period
- If used in selected patients
  1. Do not co-prescribe with opioids
  2. Use cautiously if opioid or other substance use disorders, older adults with cognitive impairment or falls risk, prior misuse of prescription medications
  3. Educate patients about adverse affects, safety issues, risk of dependency, and to not share meds
  4. Regular follow-up to assess benefits and risks
  5. Offer patient-centered tapering/discontinuation especially if not effective or harms > benefits.

Hirschtritt M, Olfson M, Kroenke K. JAMA 2021

Session 1 Q&A

Session 1: Benzodiazepine Abuse Liability, Epidemiology, and Clinical Considerations

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy

Break—15 Minutes

We are still live. Please mute your audio.

Session 2 will begin at 3:00 pm.

Session 2: Clinical, Pharmacologic, and Public Health Perspectives

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy

Janetta Iwanicki

Rocky Mountain Poison & Drug Safety

Kerri Schoedel

Altreos Research Partners

Naama Levy-Cooperman

Altreos Research Partners

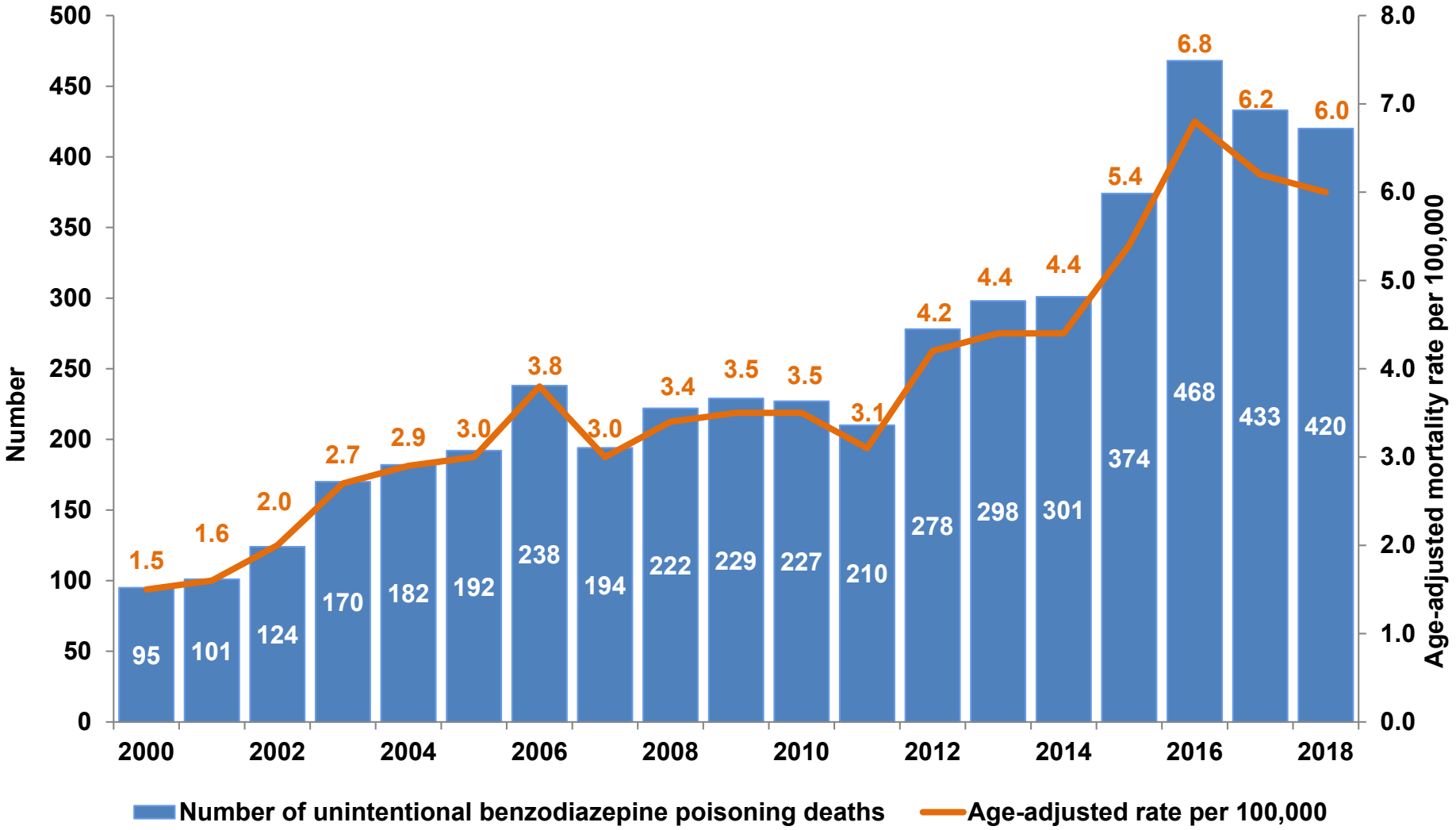
Wilson Compton

National Institute on Drug Abuse

Carla Foster

New York City Department of Health and Mental Hygiene

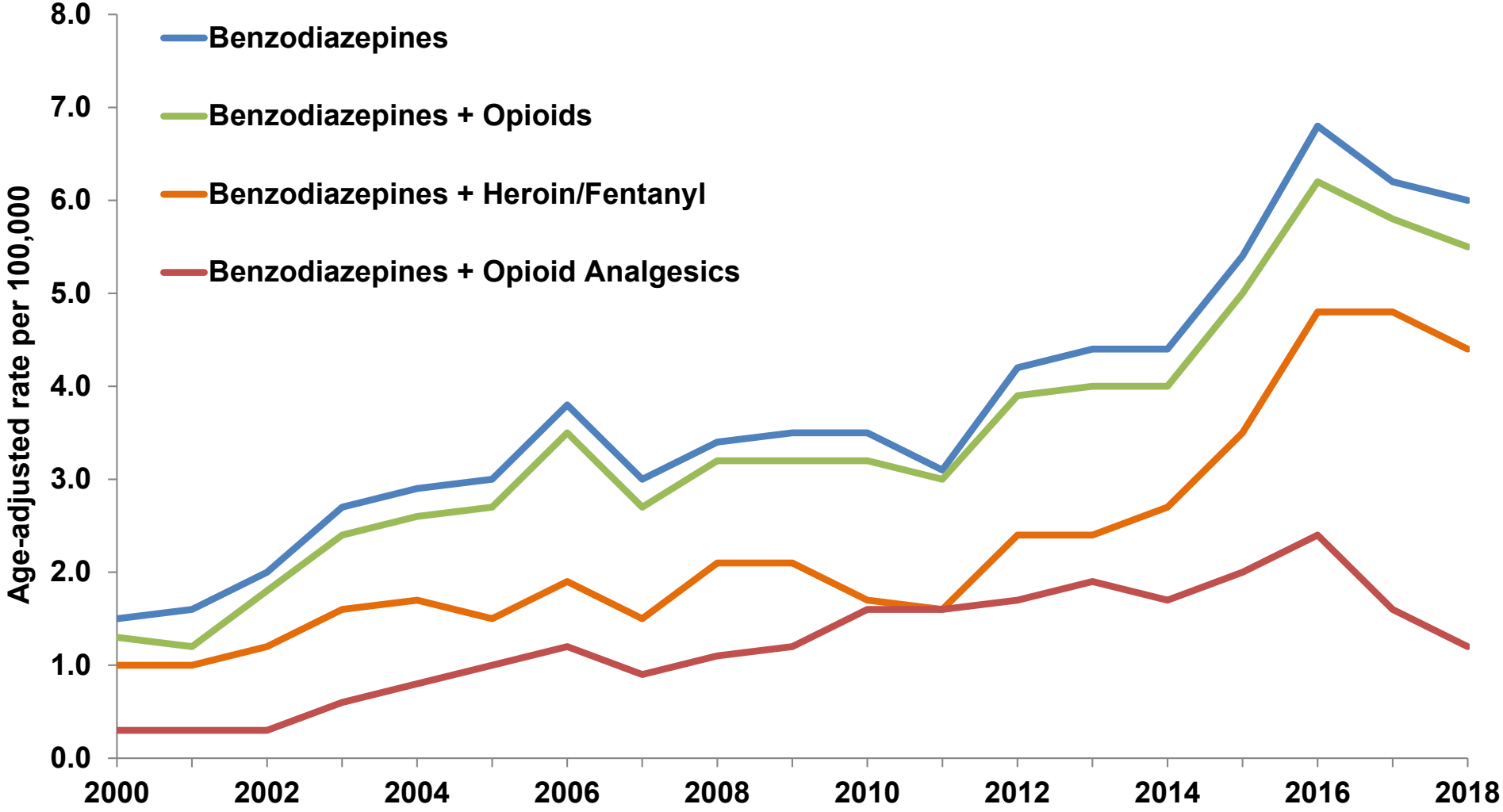
Unintentional benzodiazepine overdose deaths increased by four-fold from 2000 to 2018*



Source: New York City Office of the Chief Medical Examiner &
*New York City Department of Health and Mental Hygiene 2000-2018**
*Data for 2018 are preliminary and subject to change.

NYC Health

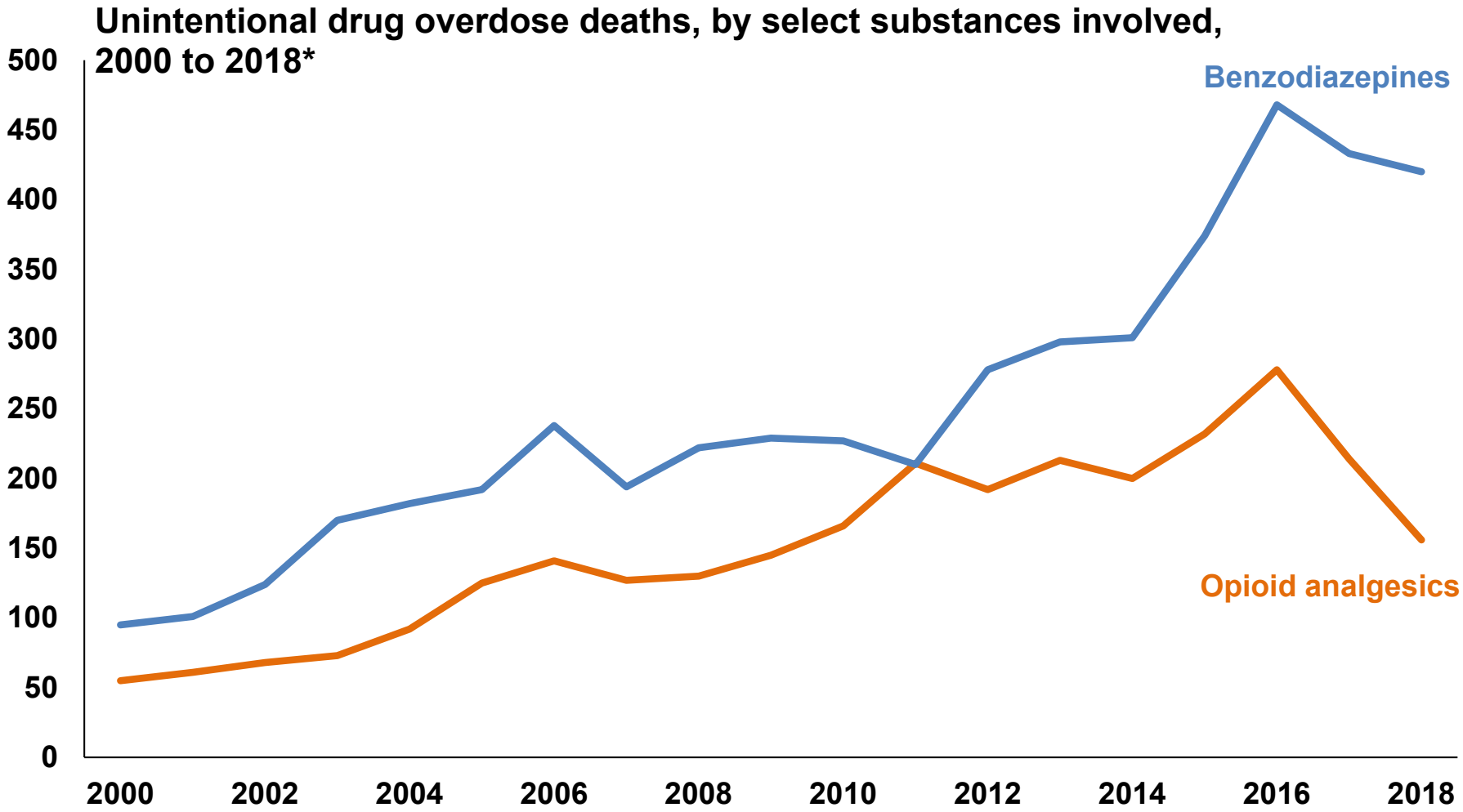
Almost all benzodiazepine overdose deaths involve opioids



Source: New York City Office of the Chief Medical Examiner &
*New York City Department of Health and Mental Hygiene 2000-2018**
*Data for 2018 are preliminary and subject to change.

NYC Health

Unintentional benzodiazepine overdose deaths continued to increase even as opioid analgesic deaths decreased



NYC Health

Kelly Clark

Addiction Crisis Solutions

Session 2 Discussion Questions

- What are the important gaps in our understanding of benzodiazepine use, misuse, abuse, and related risks?
- Many of the measurable harms associated with benzodiazepines occur in the context of polysubstance use and use disorders. How does this affect our interpretation of the risks specifically associated with benzodiazepines?
- What role do you see that prescribing practices play in decreasing and managing risks associated with benzodiazepine use?
- Based on the totality of evidence shared, do certain benzodiazepines present higher risks of misuse, abuse, or associated harms, relative to other benzodiazepines?
    - If so, what do you see as the underlying mechanism(s) or reason(s) for this increased risk?

Session 2: Clinical, Pharmacologic, and Public Health Perspectives

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy

Day 1 Adjournment

Safe Use of Benzodiazepines: Clinical, Regulatory, and Public Health Perspectives

July 12 & 13, 2021

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

Welcome Back & Day 1 Summary | Day 2

Mark McClellan

Duke-Margolis Center for Health Policy

Meeting Agenda

Day One

- Session 1: Benzodiazepine Abuse Liability, Epidemiology, and Clinical Considerations
- Session 2: Clinical, Pharmacologic, and Public Health Perspectives

Day Two

- Session 3: Health Professional and Patient Advocate Perspectives – Best Practices, Experiences, and Concerns
- Session 4: Balancing the Benefits and Risks of Benzodiazepines

Virtual Meeting Reminders

- Visit the Duke-Margolis website (https://healthpolicy.duke.edu/events) for meeting materials, including the agenda, speaker biographies, and discussion topics.

- Questions for our panelists? Feel free to submit questions via Zoom's Q&A function.

- Join the conversation @Duke-Margolis #SafeUseBenzodiazepines

Session 3: Health Professional and Patient Advocate Perspectives – Best Practices, Experiences, and Concerns

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy

Steven Wright

Alliance for Benzodiazepine Best Practices

Safe Use of Benzodiazepines:
Clinical Perspective - Best Practices

Duke-Margolis Center for Health Policy

July 13, 2021

Steven Wright, MD Littleton, CO

Family Medicine 1982
Addiction Medicine 1987
Medical Pain Management 2003

Acknowledgement

All the benzodiazepine survivors

who kept courage
when we weren’t listening

Public Domain: Edvard Munch

For most persons with BZRA - related problems

these are related to *physiologic dependence*

NOT Addiction

Blanco. BZ use, misuse, use disorders among US adults. *J Clin Psychiatry*. 2018;79(6):18m12174
Soumerai. Lack of relationship between LT BZ use & escalation to high dosages. *Psychiatr Serv*. 2003;54(7):1006-11

Disclosures

Alliance for Benzodiazepine Best Practices	Benzodiazepines
Colorado Consortium	Benzodiazepine Action Workgroup, Opioids
NEMA Research	Benzodiazepines
The Schreiber Research Group	Benzodiazepines, Opioids – Public Health
Cordant Health Solutions	Drug testing, Pharmacy services
Stader Opioid Consulting	Benzodiazepines, Opioids

Objectives

1) Outline benzodiazepine best practices

2) Highlight limiting duration of use to 2-4 weeks

3) Outline basic deprescribing best practices

BZ = Benzodiazepine
BZRA = Benzodiazepine Receptor Agonist

Benzodiazepine Best Practices Overall

- **Limit initiation: see supplemental slides**
- **Limit duration of use: 2-4 weeks**
- **Provide slow, safe, supported, shared (though patient-led) tapering to discontinue use**

Prescribing Begins with Informed Consent

- **Risks**
- **Benefits**
- **Alternatives**

Recommended:
Written informed consent document

https://www.benzoinfo.com/wp-content/uploads/2021/06/Benzodiazepine-Informed-Consent.pdf

And how to use benzodiazepines

Benzodiazepine Utility

- **Short – term efficacy has been demonstrated** [1-4]

  CBT works just as well [5,6] **…** ***and*** **… is durable 12m after completion** [7]

- **Benefit often declines after initial benefit** [2,8-15]

- **Long – term efficacy has** ***not*** **been demonstrated in research** [14-16]

- **Benzodiazepine cessation can** ***improve*** **anxiety, seizures** [17,18]

  → **Benzodiazepine - Induced Hyperanxiogenesis ?**

[1] Bandelow. Anxiety disorder Rx efficacy meta-analysis. *Int Clin Psychopharm.* 2015;30(4):183-92
[2] Locke. GAD, PD Dx & management. *Am Fam Phys.* 2015;91(9):617-24
[3] Rx anxiety disorders systematic review. Swedish Council on Health Technology Assessment. 2005.
[4] Dell'osso. BZs in psych disorders. *Eur Psych.* 2013;28(1):7-20
[5] Imai. Psych Rx v meds for PD. *Cochrane Rev.* 2016;10:CD011170
[6] Pull. Pharmacotherapy of panic disorder. *Neuropsychiatr Dis Treat.* 2008;4(4):779-95
[7] van Dis. CBT LT outcomes for anxiety-related disorders. *JAMA Psychiatry.* 2020;77(3):265-73
[8] Curran. BZ hypnotic WD in elderly. *Psychol Med.* 2003;33(7):1223-37
[9] Fava. BZ & anxiety sensitivity in PD. *Prog Neuropsychopharm Biol Psychiatry.* 1994;18(7):1163-8
[10] Fava. Fading alprazolam effects in agoraphobia. *Prog Neuropsychopharm Biol Psy.* 1988;12(1):109-12
[11] Laakmann. Buspirone, lorazepam in GAD. *Psychopharm (Berl).* 1998;136(4):357-66
[12] Nyström. Effects of LT BZ. *Nord J Psychiatry.* 2005;59(6):492-7
[13] Raffa. Basic science reasons to limit BZRA use ≤4w. *Pharmacol Pharm.* 2019;10(08):357-64
[14] Pélissolo. Anxiety, depressive disorders in 4,425 LT users. *Encephale.* 2007;33(1):32-8
[15] Westra. As-needed BZ use in anxiety. *Curr Pharm Des.* 2002;8(1):59-74
[16] Lader. BZs revisited - will we ever learn? *Addiction.* 2011;106(12):2086-109
[17] Ashton. BZ WD: outcome in 50 patients. *Br J Addict.* 1987;82:655-71
[18] Specht. DC clonazepam after LT Rx. *Epilepsia.* 1989;30(4):458-63.

Yet 80% of those

on Benzodiazepines and Z-drugs

Have been taking them for > 6 months

Kaufmann. Long-term use of benzodiazepines and nonbenzodiazepine hypnotics, 1999-2014. *Psychiatr Serv.* 2018;69(2):235-8

Benzodiazepines Best Practice Highlights

- Prescribe for indications *only* when patients are *functionally impaired*
- *Simultaneously*, prescribe alternative Rx – these take longer to begin to work
- Follow-up weekly and discontinue BZ by week 4

- Offer tapering to discontinue BZs to all on BZs > 1 month
- Initiate tapering by reducing < 5% of the original dose
- Adjust tapering amount and frequency per individual response: Patient led

- Listen, validate, and support – anticipating 12-18 months to complete

Wright. Benzodiazepine Withdrawal: Clinical Aspects. In Peppin J, Raffa R, Pergolizzi J, Wright S [Eds.]. Benzodiazepines Crisis: Ramifications of an Overused Drug Class. New York, NY: Oxford University Press, 2020

Benzodiazepine Withdrawal is Different

- Can take *far longer* than that for other substances
  Even years → Benzodiazepine Injury Syndrome

- Symptoms can be wide-ranging, severe, unusual – even seemingly bizarre
  Not due to an alternative diagnosis, nor psychosomatic

- Symptom patterns can fluctuate dramatically *unlike other substance withdrawal*
  "Waves" of worsening and "Windows" of relative relief

- Usually not due to benzodiazepine use disorder *per se* – addiction Rx not helpful
  Unlike other addiction-prone substances in which addiction is likely

[1] Ashton. The Ashton Manual: Benzodiazepines - How They Work and How to Withdraw. 2002
[2] Wright. Benzodiazepine Withdrawal: Clinical Aspects. In Peppin J, Raffa R, Pergolizzi J, Wright S [Eds.]. Benzodiazepines Crisis: Ramifications of an Overused Drug Class. New York, NY: Oxford University Press, 2020

For Benzodiazepine Survivors:

<u>This is not news</u>

Fixsen AM, Ridge D. Stories of hell and healing: internet users' construction of benzodiazepine distress and withdrawal. *Qual Health Res.* 2017;27(13):2030-41

For Researchers:

Major Questions Remain Unanswered

- > One-year studies on benzodiazepine efficacy
- > One-year studies on benzodiazepine adverse effects
- Etiology & mechanism of benzodiazepine physiologic dependence and injury
- Management of benzodiazepine discontinuation

For Prescribers:

Much of received ”Knowledge” about Benzodiazepines is Untrue

Recognize

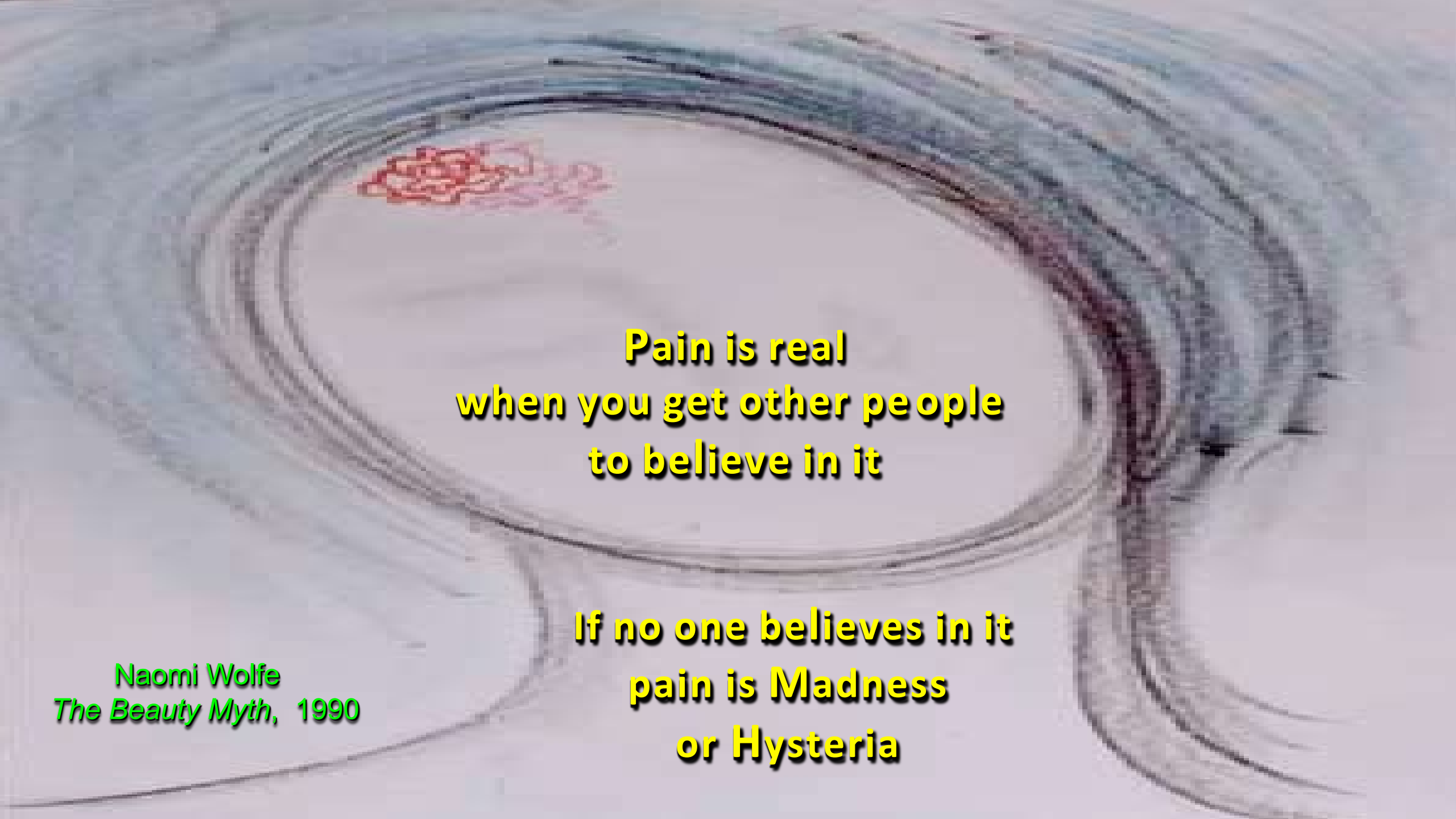
→ Acknowledge

→ Validate

→ Update

→ Engage and allow patients to lead

→ Become Benzowise


Pain is real
when you get other people
to believe in it
If no one believes in it
pain is Madness
or Hysteria
Naomi Wolfe
The Beauty Myth, 1990

sleighwright@gmail.com

benzoreform.org

Barbara Farrell

Bruyère Research Institute

deprescribing.org

Reducing medications safely to meet life's changes

Moins de médicaments, sécuritairement – pour mieux répondre aux défis de la vie

Perspective on Benzodiazepines: Best Practices, Experiences and Concerns

Barbara Farrell BScPhm, PharmD, FCSHP
Lead: Bruyère Deprescribing Guidelines Research Team
Bruyère Research Institute, Ottawa, Canada
bfarrell@deprescribing.org

INSTITUT DE RECHERCHE Bruyère RESEARCH INSTITUTE

My Geriatric Day Hospital experience

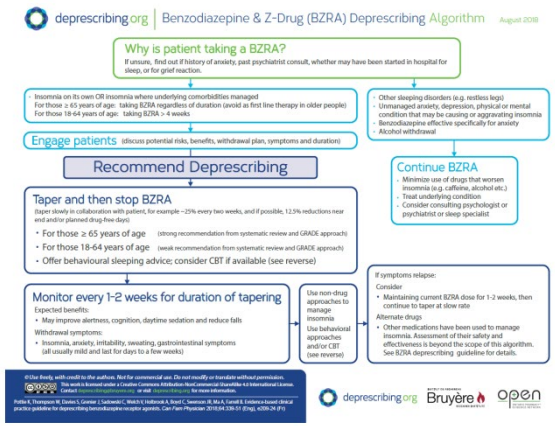
- Why people use BZRA
  - Usually started for insomnia, grief or during hospitalization
  - Often intended to be for short period but continued long-term
- The impact
  - Cognitive impairment
  - Daytime fatigue and sedation
  - Falls and fractures
  - Risk of motor vehicle accidents

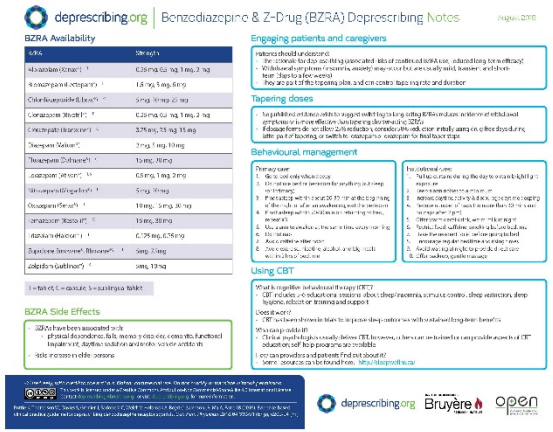
- Why it is challenging to stop
  - Withdrawal symptoms (e.g., rebound insomnia)
- The importance of understanding sleep
  - Learn about experience, modifiable sleep patterns and risk factors

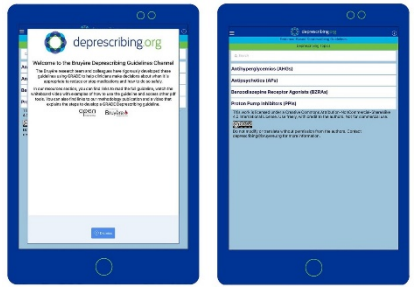
Deprescribing: tapering, withdrawal & supports

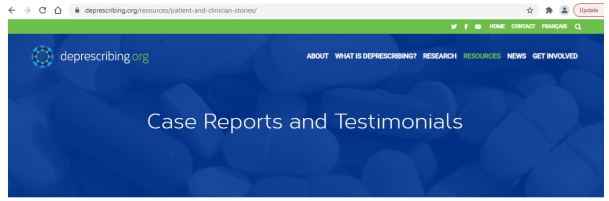
- Making the decision
  - Balancing risk vs. benefit
- Choosing a tapering plan (goal is to minimize withdrawal and help the person choose a plan that works for them)
  - Abruptly stop?
  - Taper slowly or very slowly? (no need to switch to long acting)
- Monitoring
  - Fatigue and cognitive tasks improve quickly and over 6 months
  - Expect rebound insomnia and some anxiety for a few days; check in a few days after each dose reduction or cessation (withdrawal tends to happen toward the end of tapering)
- Support
  - Avoid substances that worsen sleep or cause anxiety (e.g., caffeine)
  - Guidelines, educational pamphlets, sleep hygiene, CBTi
  - Provide reassurance that withdrawal is temporary and manageable

Useful resources







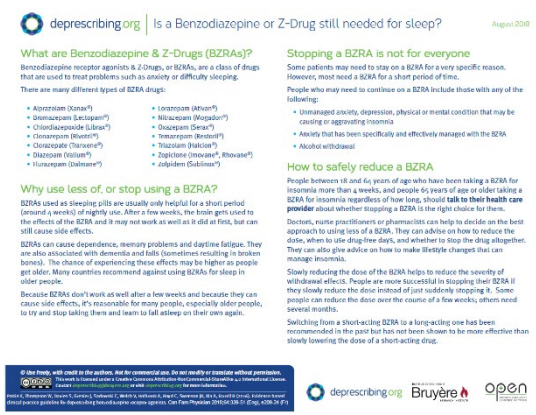


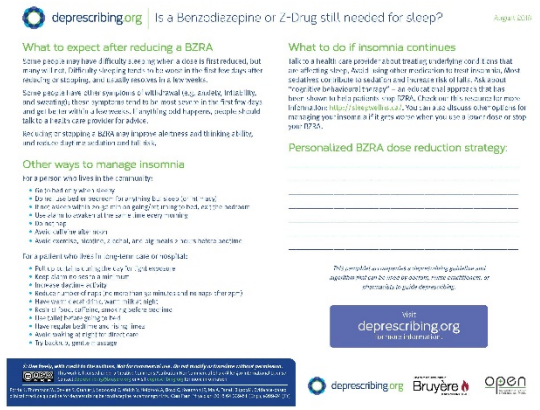
Jocelyne's Story

Over 30 years ago, Jocelyne Drouin Delovsky was prescribed clonazepam to treat her anxiety. She was told she would be on the drug for her entire life. At the time, the medication seemed like the best solution for her. As far as she could remember, she had always felt a certain level of anxiety. As time went on however, Jocelyne still didn't feel quite right – despite her continued use of the medication.

She continued the drug for many years. Whenever her anxiety started to return she would take another pill. It wasn't until Jocelyne was in her sixties that she considered stopping her use of clonazepam.

Working together with her family physician, Jocelyne was able to taper off and eventually stop her use of clonazepam. She found alternative support in therapy to help manage her anxiety. This was



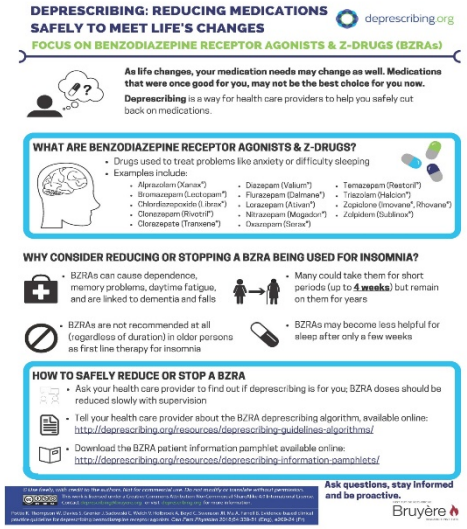


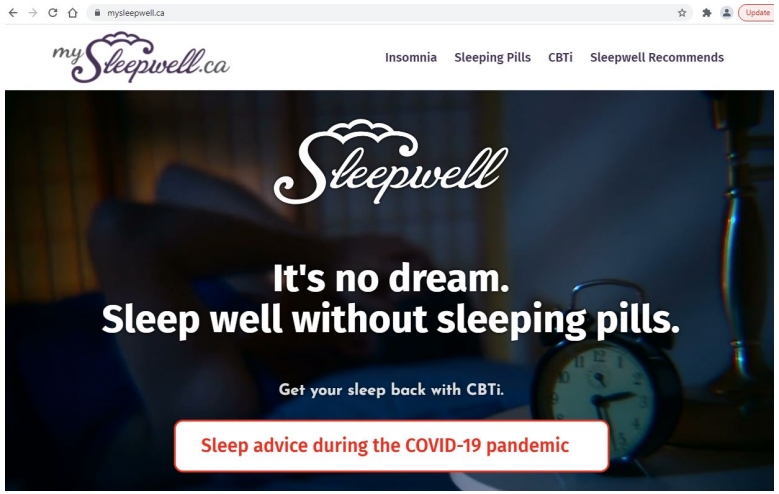
https://deprescribing.org/

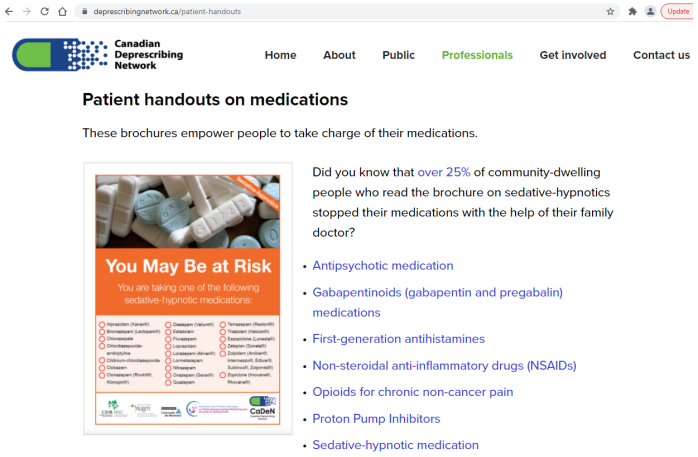
INSTITUT DE RECHERCHE Bruyère RESEARCH INSTITUTE

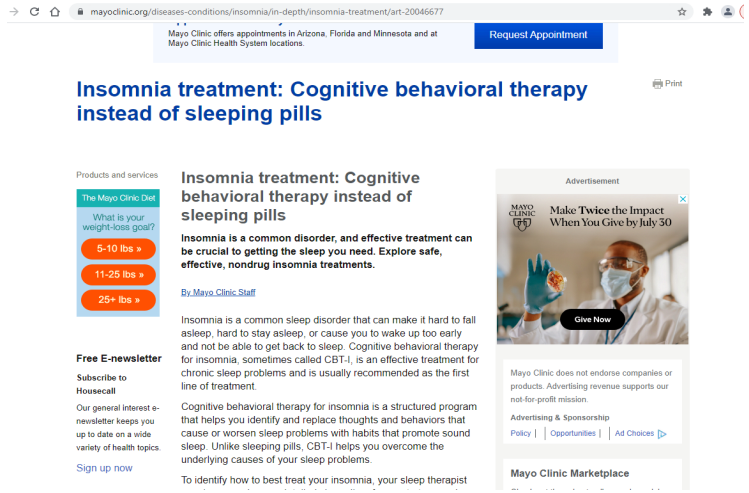
deprescribing.org

Useful resources

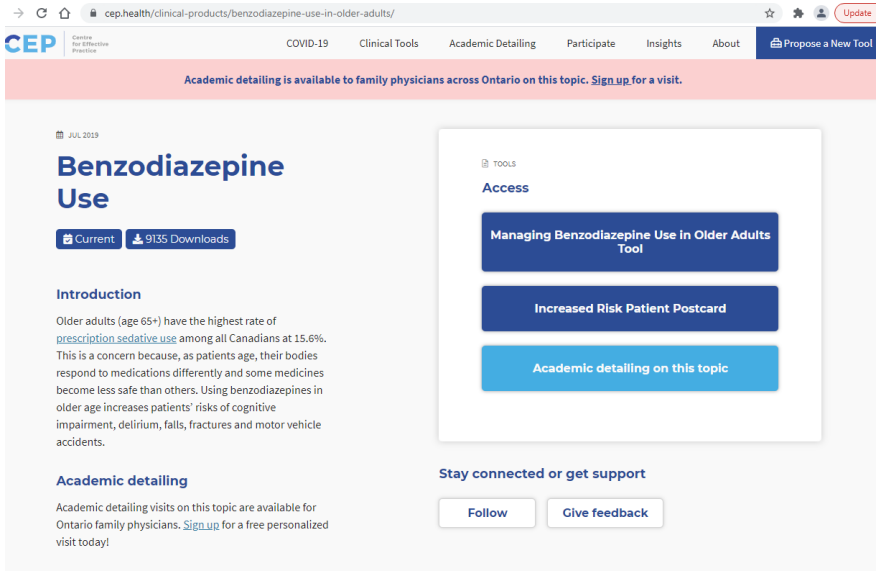


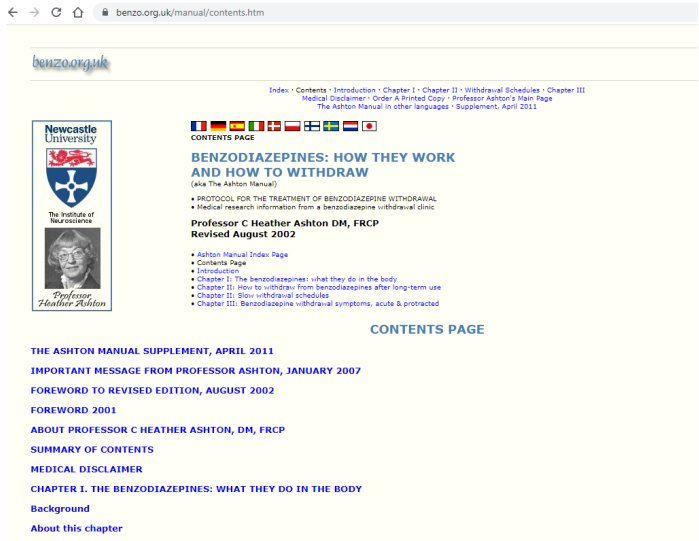






Useful resources





How we could avoid chronic BZ use

- Begin with the end in mind
  - BZRA is a temporary strategy (e.g., 7 days)
  - Use low doses
  - Decide on the ‘exit plan’ up front
  - Prescribe small amounts (e.g., 7 tablets)
  - Establish non-pharm strategies
- In hospital
  - Safe sleep protocols (e.g., limit interruptions, noise, light)
  - Education for staff and prescribers
  - Remove BZRA from admission order set
  - Limit discharge Rx quantities and provide deprescribing plan

Sangeeta Tandon

U.S. Food and Drug Administration

Stakeholder Engagement: Benzodiazepines

Duke Margolis Meeting
July 13, 2021

Sangeeta Tandon, PharmD, MPH
Professional Affairs and Stakeholder Engagement (PASE)
Office of the Center Director
Center for Drug Evaluation and Research (CDER)

Disclaimer

This presentation reflects the views of the author/presenter and should not be construed to represent FDA's views or policies.

Objectives

- Discuss the role of Professional Affairs and Stakeholder Engagement within FDA/CDER
- Describe Network of Experts and Safe Use Initiative
- Discuss expert opinions regarding benzodiazepine prescribing practices
- Introduce Safe Use Initiative research funding opportunities

What is PASE's function?

PASE promotes a culture of engagement within CDER by facilitating the exchange of information between CDER Offices/Divisions and external stakeholder groups.

Internal CDER Stakeholders

CDER Leadership & Offices

PASE

External Stakeholders (non-regulatory)

- *Patient Advocacy Groups*
- *Chain Pharmacies, PBMs, etc.*
- *HCP Professional Organizations*
- *Patient Safety Groups*
- *Researchers in Harm Reduction*
- *State Regulatory Boards*
- *Federal Partners*

PASE Mission

- Enrich the experience of patients, advocacy groups, health care professionals, and agencies in engaging with CDER.
- Improve our stakeholders' drug regulatory insight and understanding.
- Enhance safe use of medications and reduce preventable harm from medication misuse, abuse and errors.

Network of Experts (NoE)

- Facilitates collaborations and exchanges between CDER scientists and experts associated with external organizations
- Consists of a vetted network of partner organizations and their member scientists, clinicians and engineers
- Provides the FDA rapid access to expertise when it is needed to supplement existing knowledge and expertise
- The NoE is **not** a replacement for existing mechanisms for obtaining external scientific or clinical expertise (i.e.- advisory committees, special government employees (SGEs), public meetings)

https://www.fda.gov/about-fda/center-devices-and-radiological-health/network-experts-program-connecting-fda-external-expertise

Network of Experts: Request for Feedback

- FDA requested that experts give feedback on their experience regarding:
  - Approach to prescribing benzodiazepines
  - Clinical Guidelines or Support Tools currently available to inform decision-making
  - Prescriber and Patient Education and Resources
  - COVID-19 effects on decision-making about prescribing practices
  - Awareness of the Safety Labeling Change and Drug Safety Communication FDA issued on benzodiazepines - September 2020

Network of Experts: Identified Experts

- 4 experts volunteered to speak on topic of benzodiazepine prescribing practice in the United States
  - 3 geriatricians
  - 1 psychiatrist with subspecialty in addiction medicine

Themes Identified through NoE calls by Experts

- All experts expressed limited use of benzodiazepines in their practice and often avoiding benzodiazepines, if possible
  - Little to no distinction between benzodiazepines compared to z-hypnotics from a risk perspective in their decision for prescribing
- Overall consensus is that there are no evidence-based guidelines for tapering benzodiazepines. Tools for negotiating a benzodiazepine taper are lacking.
- Three out of four prescribers identified educational tools for their primary care physician peers as an area of need
  - Concerns about initiating benzodiazepines inappropriately or in a suboptimal way.

Themes Identified: Pandemic-related Prescribing Practices

- COVID-19 affected decision-making about prescribing practices of benzodiazepines:
  - “enormous spikes in phone calls and requests and people begging us for medications to help calm anxious ones who weren’t able to have usual routines”
  - Threshold to prescribe was lower
  - More hesitant to deprescribe medications in a virtual environment

Themes Identified: Awareness of Safety Labeling Changes

- Benzodiazepine Safety Labeling Change & Drug Safety Communication - September 2020
- Boxed Warning was updated to include the risks of
  - abuse, misuse, addiction, physical dependence and withdrawal reactions to help improve their safe use.

https://www.fda.gov/media/142368/download

Themes Identified: Awareness of Safety Labeling Changes

- Experts reported either being unaware or having limited recall of safety labeling change
  - **One expert** was unaware of labeling change. Expert cited that 8 prescriber colleagues were unaware of the change as well.
  - **Three experts** were aware
    - Two of those experts could not recall the content or the wording of the safety communication
    - All experts indicated their practice did not change because these prescribers identified themselves as being “cautious” or “tight in prescribing practices” already

Information Dissemination of Safety Labeling Change

- How was this information disseminated?
  - Drug Safety Communication
  - Press release
  - Messages to a variety of different listserv groups that included Drug Info listserv and Trade Press listserv.
  - Communication also went out via social media

Insights Expressed by NoE experts

- Prescribers identified a need for evidence-based tools for tapering benzodiazepines
- Pandemic impacted prescribing patterns of benzodiazepines
- Little to no distinction between benzodiazepines compared to z-hypnotics from a risk perspective in prescriber's decision-making
- Identified a need for resources for primary care physicians who may initiate patients on benzodiazepines inappropriately
- One expert identified that neither her nor her peers were aware of the Safety Labeling Change

→ Are there additional ways to disseminate labeling changes to prescribers?

Safe Use Initiative

- Mission is to create and facilitate public and private collaborations within the healthcare community
- Goal is to reduce preventable harm by
  - identifying specific, preventable medication risks
  - developing, implementing and evaluating cross-sector interventions with partners who are committed to safe medication use
- Solicits and funds research projects that align with mission and goal

https://www.fda.gov/drugs/drug-safety-and-availability/safe-use-initiative

Current Safe Use Projects

- Safe Use has 8 current projects.
- Safe Use has funded 26 projects involving a wide variety of drugs and potential adverse events.
  - Opioids
  - Anticoagulants
  - Antibiotics
  - Anti-hyperglycemic agents
  - Stimulants
  - Pediatric cough and cold medications
  - NSAIDS

https://www.fda.gov/Drugs/DrugSafety/SafeUseInitiative/ucm277720.htm

Safe Use Partners

- Healthcare professionals and professional societies
- Pharmacies, hospitals, and other health care entities
- Patients, caregivers, consumers, and their representative organizations

= Almost anyone

Contact:
CDERSafeUseInitiative@fda.hhs.gov

Questions?

Email: Sangeeta.Tandon@fda.hhs.gov

Chinyere Ogbonna

Kaiser Permanente

Sumit Agarwal

Brigham and Women's Hospital

Christy Huff

Benzodiazepine Information Coalition

GAPS IN PHYSICIAN EDUCATION

- Stopping benzodiazepines abruptly or tapering too quickly
  - Best practice is a flexible, gradual taper plan tailored to patient symptoms
  - May take months or years
- Not recognizing adverse effects (i.e. tolerance, physical dependence, and withdrawal)
  - Assumed to be return of original condition or new illness
  - Leads to unnecessary testing and treatment, polydrugging
- Conflation of addiction with physical dependence
- Lack of informed consent
- Little awareness of protracted withdrawal syndrome

BENZODIAZEPINE INJURY SYNDROME

- A subset of patients (10-15%) withdrawing from benzodiazepines experience a protracted course (lasting years, possibly permanent in some cases) [1]
- Symptoms can be disabling, and often present in a pattern of ”waves and windows”[2]
- Relentless nature of symptoms, plus lack of support/treatment increases risk of suicide
- Long-term use of benzodiazepines can alter conformation of the GABA receptor, causing functional changes in the nervous system
- Further research is need to determine who is at risk
  - Abrupt cessation/rapid taper
  - Kindling phenomenon
  - Genetics

1. Ashton H. J Subst Abuse Treat 1991;8:19-28.

2. Wright S. Benzodiazepine withdrawal:Clinical aspects. In: *The Benzodiazepines Crisis: The Ramifications of an Overused Drug Class*. New York, NY: Oxford University Press; 2020:117-148.

Scott Winiecki

U.S. Food and Drug Administration

Session 3 Discussion Questions

- How do health professionals currently approach prescribing, tapering, and discontinuing benzodiazepines to address the risks of abuse, addiction, physical dependence, and withdrawal reactions? How are non-pharmacologic treatments used in conjunction with benzodiazepines or as alternatives to benzodiazepines?
- What are the barriers to and facilitators of safe use of benzodiazepines for patients and health professionals? What are some opportunities to improve benzodiazepine prescribing practices?
- What resources do health professionals rely on to inform their approach? What gaps exist in education about benzodiazepines for patients and health professionals?
- If access to benzodiazepines, or some subset of this drug class, were further restricted in some way due to concerns related to misuse and abuse, what do you see as potential unintended consequences?

Session 3: Health Professional and Patient Advocate Perspectives – Best Practices, Experiences, and Concerns

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy

Break—15 Minutes

We are still live. Please mute your audio.

Session 4 will begin at 3:00 pm.

Session 4: Balancing the Benefits and Risks of Benzodiazepines

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy

Kurt Kroenke

Indiana University School of Medicine

Wilson Compton

National Institute on Drug Abuse

Chinyere Ogbonna

Kaiser Permanente

Christy Huff

Benzodiazepine Information Coalition

Marc Stone

U.S. Food and Drug Administration

Marta Sokolowska

U.S. Food and Drug Administration

Session 4 Q&A

Session 4: Balancing the Benefits and Risks of Benzodiazepines

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy

Closing Remarks & Meeting Adjournment

Mark McClellan

Duke-Margolis Center for Health Policy

Thank You!

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