Co-prescribing benzodiazepines to patients receiving opioids: potential risks and benefits

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EXCEPTIONAL CARE. WITHOUT EXCEPTION.

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CDC Guideline for Prescribing Opioids for Chronic Pain

"Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible."

Dowell et al., *MMWR Recomm Rep*, 2016

Prevalence of co-prescribing

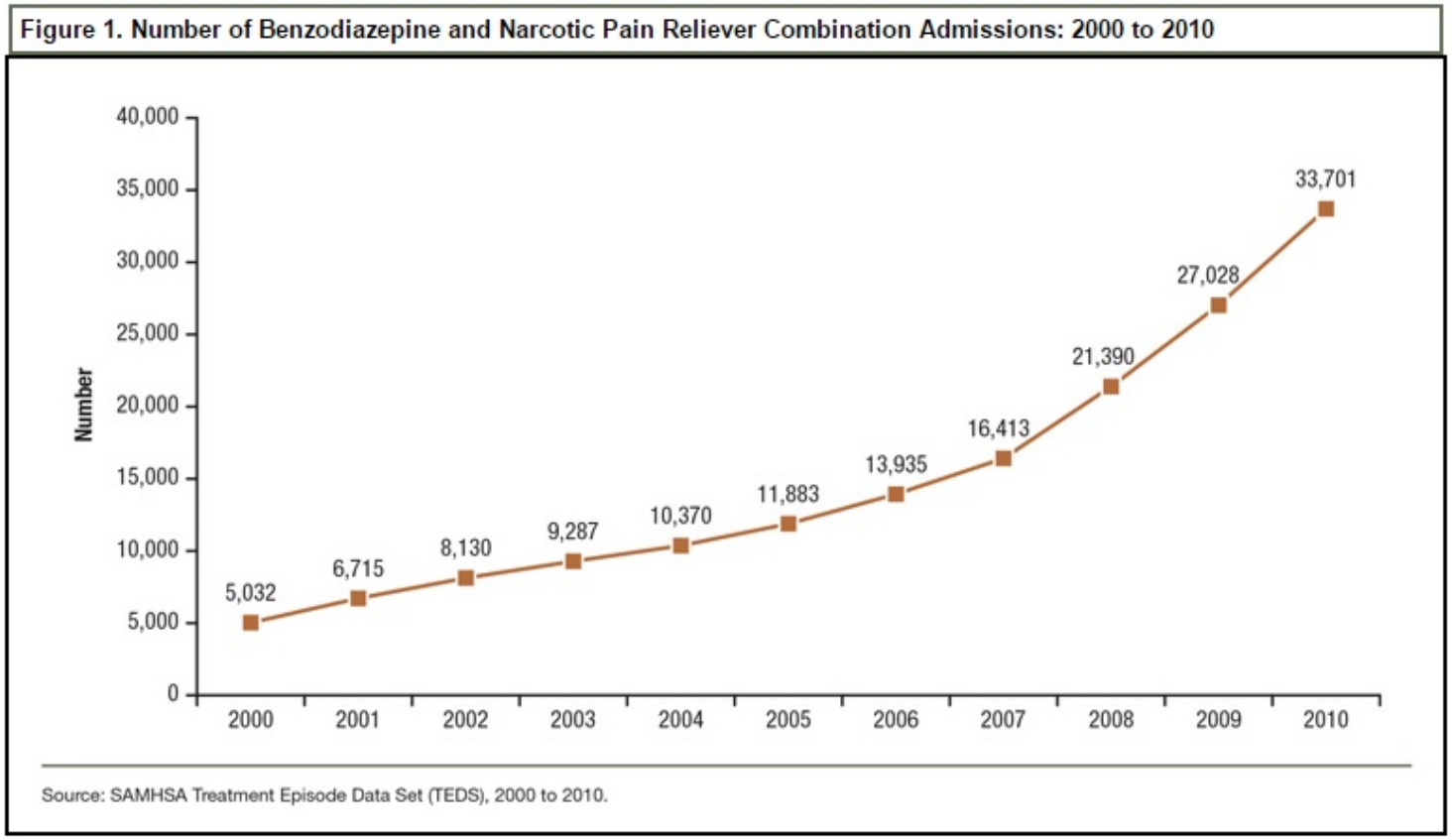
From 2002 to 2014, among opioid recipients co-prescribing increased 41% from 6.8% to 9.6%[1]

Between 2001 to 2010, benzodiazepines were co-prescribed at 16% of chronic pain visits[2]

Benzodiazepine use more common in those with SUD history[3] and higher opioid doses[4]

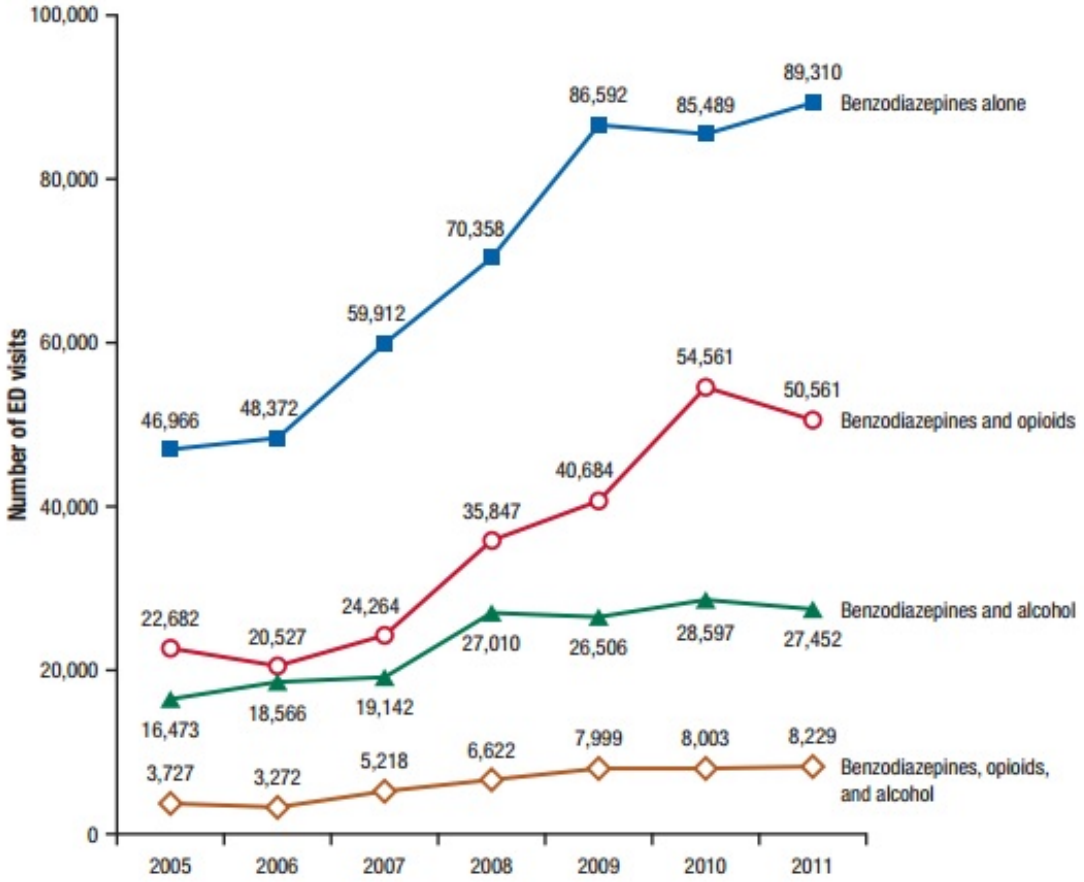
[1]Hwang et al., *Am J Prev Med*, 2016
[2]LaRochelle et al., *Pharmacoepidemiol Drug Saf*, 2015
[3]Neilsen et al., *Pain Med*, 2015
[4]Morasco et al., *Pain*, 210

SUD treatment admissions



SAMHSA, 2012

ED visits



SAMHSA, 2014

Benzodiazepines and overdose mortality

	Hazard ratio	95% CI
Benzodiazepine exposure		
None	1.00 (ref)	-
Currently prescribed	3.72	3.36-4.12
Benzodiazepine dose		
>0-10	1.00 (ref)	-
>10-20	1.59	1.34-1.90
>20-30	2.27	1.86-2.79
>30-40	2.47	1.96-3.11
>40	2.93	2.29-3.76

Park et al., *BMJ*, 2015

Risks of co-prescribing

Co-prescribing associated with increased risk of overdose in privately insured patient population[1]

Co-prescribing associated with self-inflicted and violence-related injury and all-cause mortality[2]

[1]Sun et al., BMJ, 2017
[2]Gressler et al., Pain, 2018

Other risks of benzodiazepine use

Systematic review: 5 out of 5 studies examining BZD use in Alzheimer's disease found BZDs associated with cognitive deterioration[1]

Systematic review: 6 out 7 studies found association between BZD use and increased risk of hip fracture[2]

[1]Defrancesco et al., *Int J Neuropsychopharmacol*, 2015
[2]Cumming et al., *CNS Drugs*, 2003

Co-prescribing since CDC guidelines

CDC guideline release associated with an increased rate of decline in co-prescribing[1]

Co-prescribing rates modestly decreased after CDC guideline release[2]

- But for those who continued to be co-prescribed, proportion of overlapping co-prescribing days did not change

Co-prescribing rates reduced after FDA boxed warning against co-prescribing in 2016, but still substantial co-prescribing[3]

[1]Bohnert et al., *Ann Intern Med*, 2018
[2]Jeffrey et al., *JAMA Netw Open*, 2019
[3]Zhu et al., *JAMA Psychiatry*, 2019

Anxiety and chronic pain

Anxiety disorders are common in chronic pain patients

- 35% of those with chronic pain in one large population-based study[1]

Anxiety severity was adversely associated with pain severity and pain-related disability in two longitudinal studies[2,3]

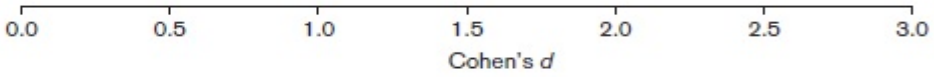
Anxiety is associated with increased risk of prescription opioid misuse[4,5]

[1]McWilliams et al., *Pain*, 2003
[2]Bair et al., *Clin J Pain*, 2013
[3]Lerman et al., *Psychosom Med*, 2015
[4]Arteta et al., *Pain Med*, 2016
[5]Lee et al., *J Subst Use*, 2019

Efficacy of benzodiazepines

Meta-analysis for GAD, panic disorder, and SAD

Treatment	*n*	*d*
SNRIs	23	2.25
Benzodiazepines	42	2.15
CBT + drug	16	2.12
SSRIs	62	2.09
TCAs	15	1.83
Relaxation	17	1.36
CBT/exposure, individual	93	1.30
Pill placebo	111	1.29
CBT, group	18	1.22
Psychodynamic therapy	5	1.17
Non-face-to-face therapies	34	1.18
Psychological placebo	16	0.83
Waiting list	50	0.20



Bandelow et al., *Int Clin Psychopharmacol*, 2015

Advantages of benzodiazepines

Good tolerability

Fast onset of action

Can use for as-needed treatment

Problems with other treatments

Non-benzodiazepine anxiolytics (e.g. SSRIs, buspirone)

- Tolerability
  - Anxiety
  - Insomnia
  - Nausea
  - Sexual dysfunction
- Slow onset of action
- Withdrawal syndrome

Psychotherapies

- Significant barriers to dissemination
- Intervention length

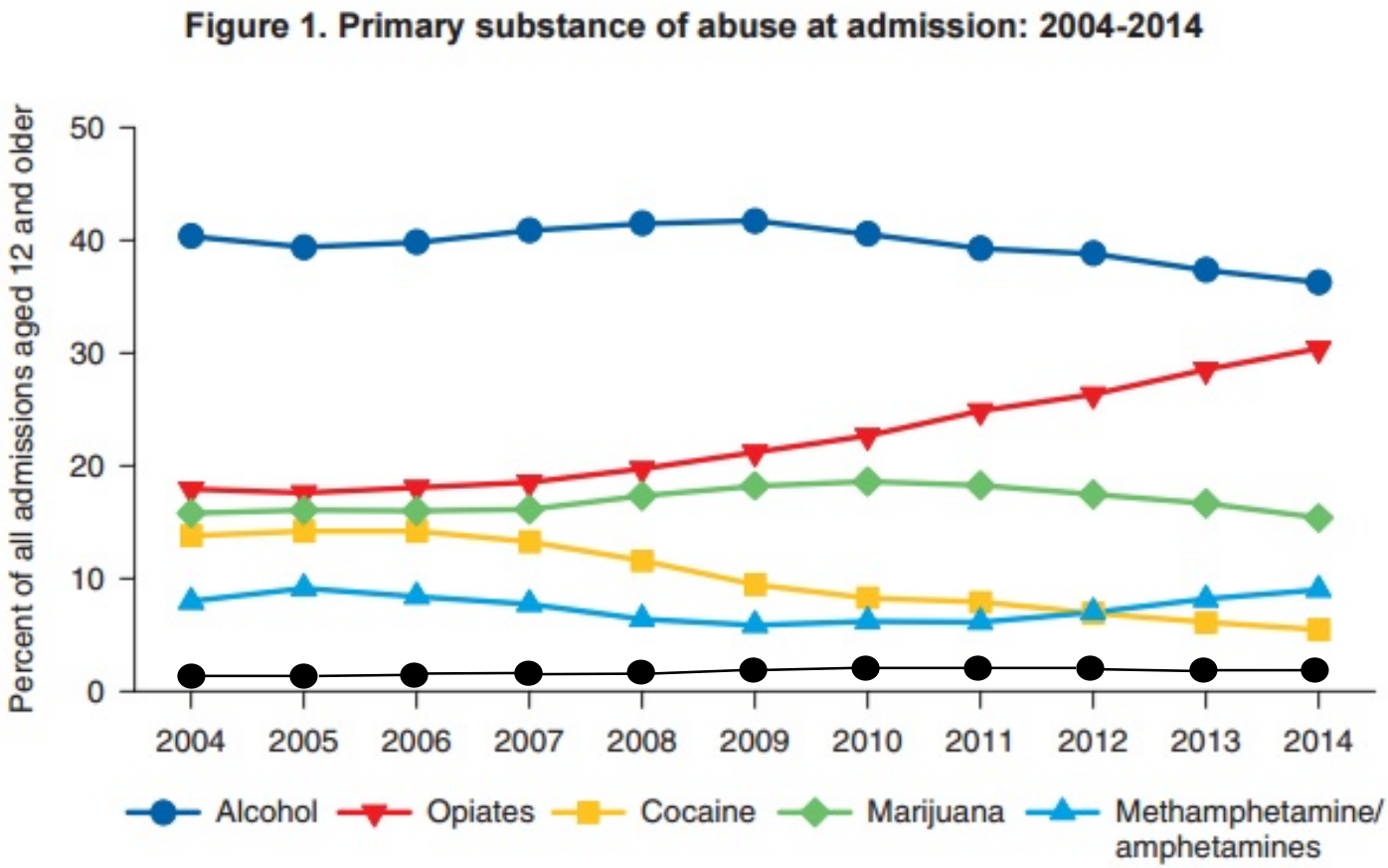
Risk of benzodiazepine addiction

Figure 2 Table. Percentages of Year-Before-Last Initiates Who Were Dependent on the Initiated Substance in the Past Year, by Substance: 2004-2006

Substance	Percent
Heroin	13.4%
Crack**	9.2%
Marijuana	5.8%
Stimulants*	4.7%
Cocaine (Not Including Crack)**	3.7%
Alcohol	3.2%
Pain Relievers*	3.1%
Sedatives*	2.4%
Hallucinogens	1.9%
Tranquilizers*	1.2%
Inhalants	0.9%

Source: SAMHSA, 2004-2006 NSDUHs.

Treatment admissions for benzodiazepines



TEDS, 2016

Survey of prescribers

Reasons for co-prescribing

- Not enough time to negotiate discontinuation
- Patient is stable
- Lack of information on other treatments, particularly behavioral

Discontinuing benzodiazepines will be:

- Too difficult
- Make patients suffer

>30% of prescribers perceived negative or extremely negative changes for patients after long-term benzodiazepine therapy was discontinued

Hawkins et al., *Pain Med,* 2017

Co-prescribing in patients receiving buprenorphine

	Adjusted hazard ratio	95% CI
Non-fatal opioid overdose	2.05	1.68-2.50
Fatal opioid overdose	2.92	2.10-4.06
All-cause mortality	1.90	1.48-2.44
Buprenorphine discontinuation	0.87	0.85-0.89

Park et al., Addiction, 2020

Qualitative study of OUD patients and providers

OUD patients used benzodiazepines both appropriately and inappropriately

Patients learned to use benzodiazepines safely and were more able to do so when stable in OUD treatment

Patients commonly aspired to discontinue benzodiazepines

Patients prioritized the benefits of benzodiazepine therapy and providers prioritized the risks

Park et al., *Subst Abus*, 2019

Tapering benzodiazepines

Gradual benzodiazepine taper is more effective than routine care

Adding a psychosocial intervention to the taper helps patients complete the taper and continue to be benzodiazepine-free at later follow-up

Oude Voshaar et al., *Br. J. Psychiatry*, 2006
Gould et al., *Br. J. Psychiatry*, 2014

Summary

Co-prescribing has declined since release of CDC guidelines for prescribing opioids for chronic pain yet is still common

Prescribing benzodiazepines potentially has both risks and benefits in patients receiving opioids

More guidance is needed to help clinicians minimize the risks of co-prescribing and how to safely and effectively taper benzodiazepine use