Opioid and benzodiazepine co-prescribing and mortality among Veteran Affairs patients with posttraumatic stress disorder

Eric Hawkins, PhD

Carol Malte, MSW

Center of Excellence in Substance Addiction Treatment and Education (CESATE)

Agenda

- Review risks of concurrent opioid and benzodiazepine use
- Describe relevance and risks of these medication classes in PTSD
- Highlight limitations of prior research on risks associated with concurrent opioid and benzodiazepine use
- Present the findings of a study designed to assess the comparative safety of opioid and benzodiazepine co-prescribing among Veterans with PTSD

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Co-Investigators

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Andrew Saxon, MD

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Scott Coggeshall, PhD

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The views expressed reflect the opinions of the authors and not the Department of Veterans Affairs

Poll Question #1

What is your primary role in VA?

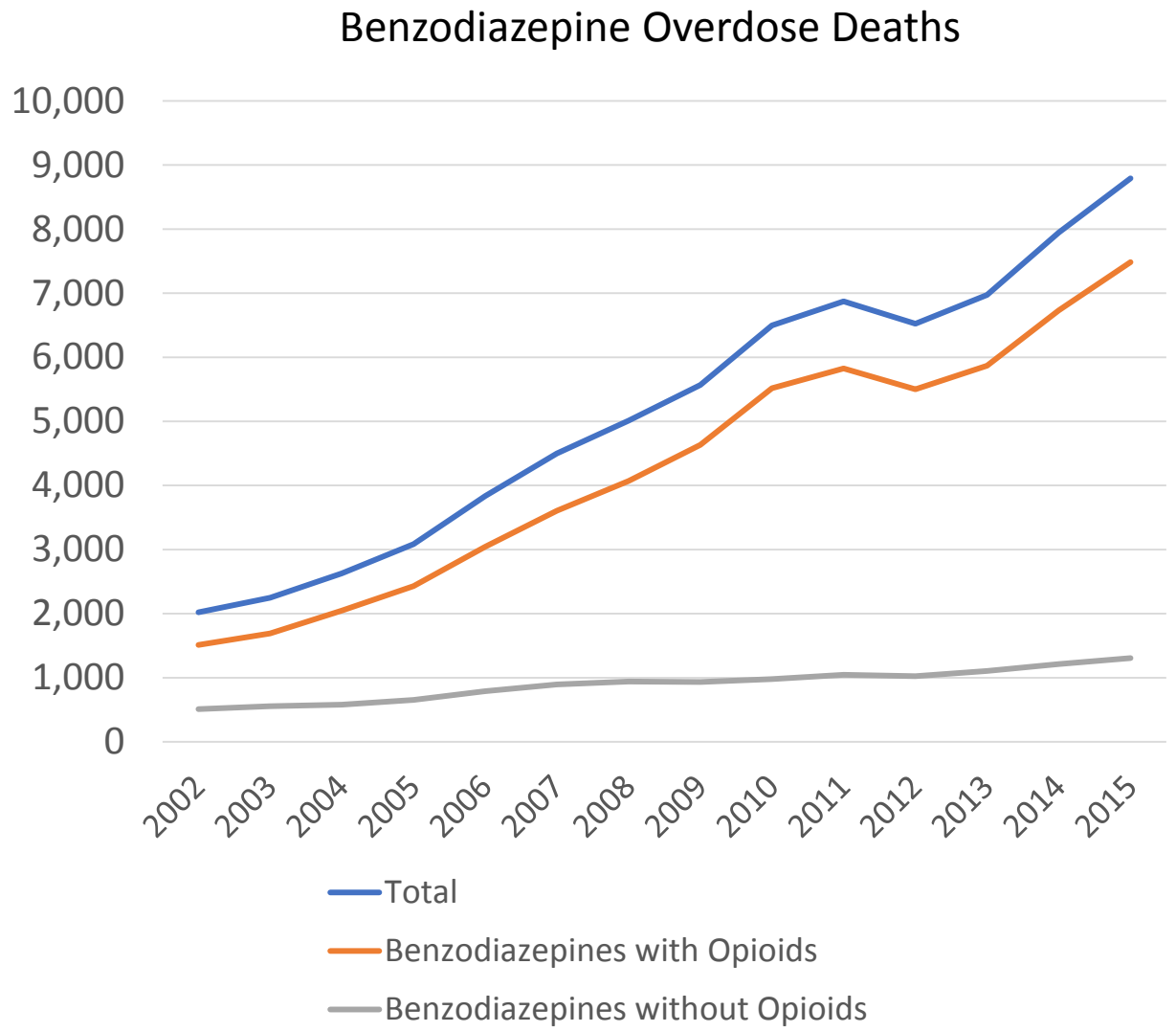
- Prescribing clinician
- Non-prescribing clinician
- Researcher
- Administrator, manager, or policy-maker
- Other

Poll Question #2

- Which best describes your experience with opioid and/or benzodiazepine prescribing?
  - Have not been involved in opioid and/or benzodiazepine prescribing
  - Prescribe opioids and/or benzodiazepines to my patients
  - Provide clinical care to patients who are prescribed opioids and/or benzodiazepines
  - Part of research team examining opioid and/or benzodiazepine prescribing

Background

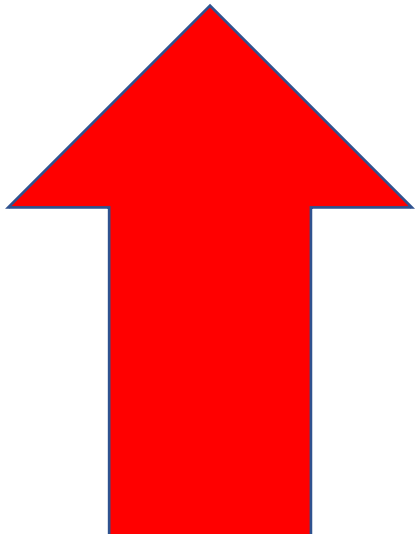
- Pharmaceutical overdose deaths have increased dramatically over the last 16 years
- Opioids and benzodiazepines are the most common prescription classes involved in pharmaceutical overdoses
- From 2002 to 2015, there has been a 4-fold increase in benzodiazepine overdose deaths that also involve opioids



Rudd et al., MMWR, 2016; NIDA, Accessed 5/21/2018; Bachhuber, AJPH, 2016

Background

- Taken independently, these two medication classes increase risk of overdose
- When used in combination, respiratory depressant effects of these medications likely interact to further increase overdose risk
- Focus on overdose deaths likely underestimates mortality risk of these medications



RISK

Rudd et al., MMWR, 2016; Bachhuber, AJPH, 2016; White, Addiction, 1999.

Risks of concurrent opioid and benzodiazepine use

- These medication classes are associated with increased risks of:
  - Fall-related injuries among elderly
  - Motor vehicle accidents
- Emerging evidence suggests that opioids and benzodiazepines may be associated with increased risk of death due to circulatory and respiratory disease

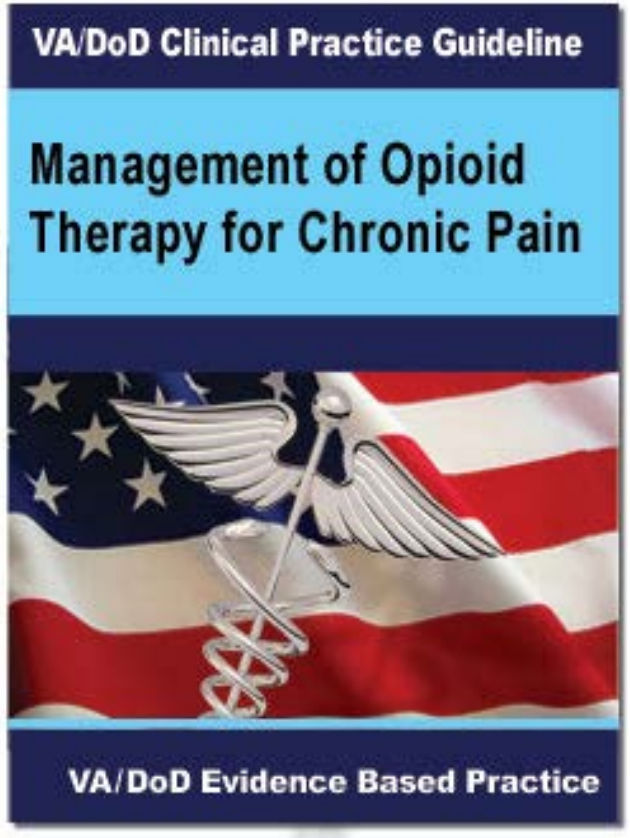
Woolcott et al., Arch Intern Med, 2009; Smink et al., *CNS Drugs,* 2010; Ray et al., JAMA, 2016; Vozoris et al., Eur J Clin Pharm, 2017; Ekstrom et al., BMJ, 2014

Comparative Safety of Medication Classes

- Despite mortality risk associated with these medication classes, few studies have assessed the comparative safety of co-prescribing opioids and benzodiazepines to:
  - Opioids only
  - Benzodiazepines only
  - Neither medication class

Psychiatric Conditions and Co-prescribing

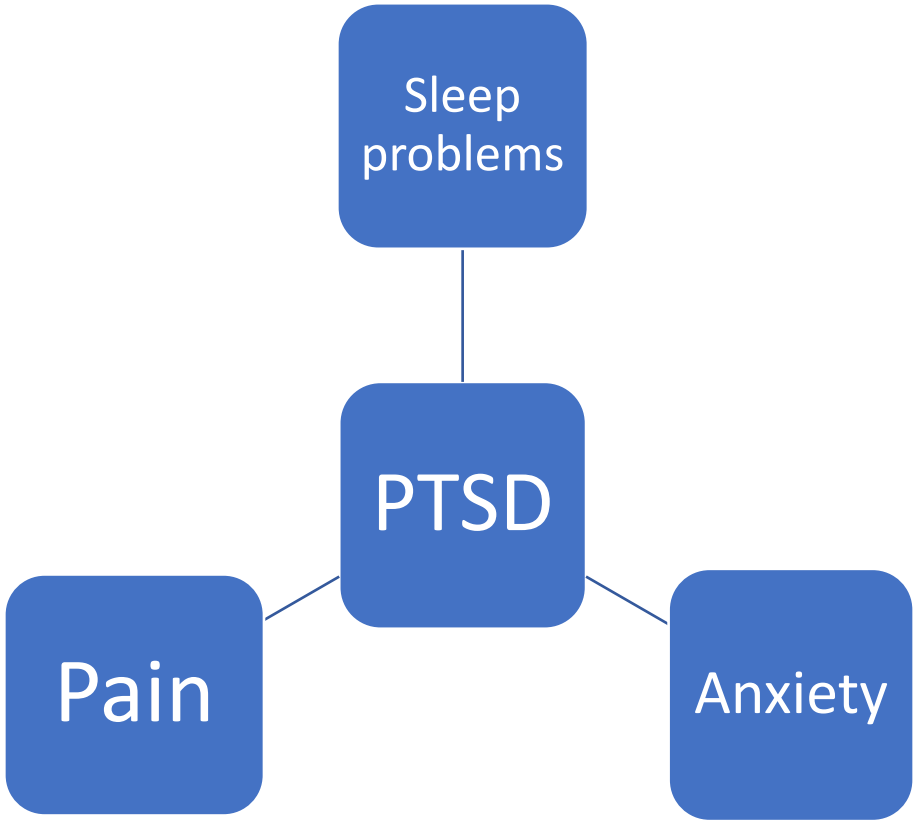
- VA/DoD clinical practice guidelines discourage dual use of these medication classes
- However, dual use is common among those with psychiatric disorders, such as posttraumatic stress disorder (PTSD)



Park et al., BMJ, 2015; Lund, et al., J Clin Psych, 2012; VA/DoD CPG for Management of Opioid Therapy for Chronic Pain, 2017

PTSD and Co-prescribing

- Patients with PTSD present with multiple and complex chronic symptoms
  - Symptoms often treated with opioid and benzodiazepine medications
- These medications may pose serious harm due to abuse potential and side effects, particularly for those with PTSD
  - Increased risk of circulatory and respiratory disease



Hoffman et al., Mt. Sinai J. Medicine, 2008; Reimann et al., Sleep Med Rev, 2009; Schwartz et al., Psychosom, 2006; Cohen et al., Am J Hypertens. 2015; Boscarino, Psychosom Med, 1997

Characteristics of Prior Research

- Most studies examining the risks of concurrent opioid and benzodiazepine use have
  - Focused on overdose risk
  - Used prevalent user designs
  - Controlled confounding via analyses vs. design (e.g., covariate adjustment)
- This study was designed to address these limitations

Questions

Using an incident user design and balancing patient characteristics (e.g., demographics, clinical diagnoses, medications, utilization):

- Is there a short-term mortality risk associated with new concurrent receipt of benzodiazepine and opioid prescriptions among Veteran patients with PTSD,
  - relative to patients who receive new single medication therapies or no medications?
- Is there a relative risk of death by circulatory-related disease, respiratory-related disease and overdose in the short-term?

Study Aims

- What is the relative risk of all-cause mortality among those newly co-prescribed opioids and benzodiazepines relative to those
  - newly prescribed benzodiazepines only?
  - newly prescribed opioids only?
  - not prescribed drugs from either of these medication classes
- Second, what is the relative risk of death by overdose, circulatory- and respiratory-related causes

Methods

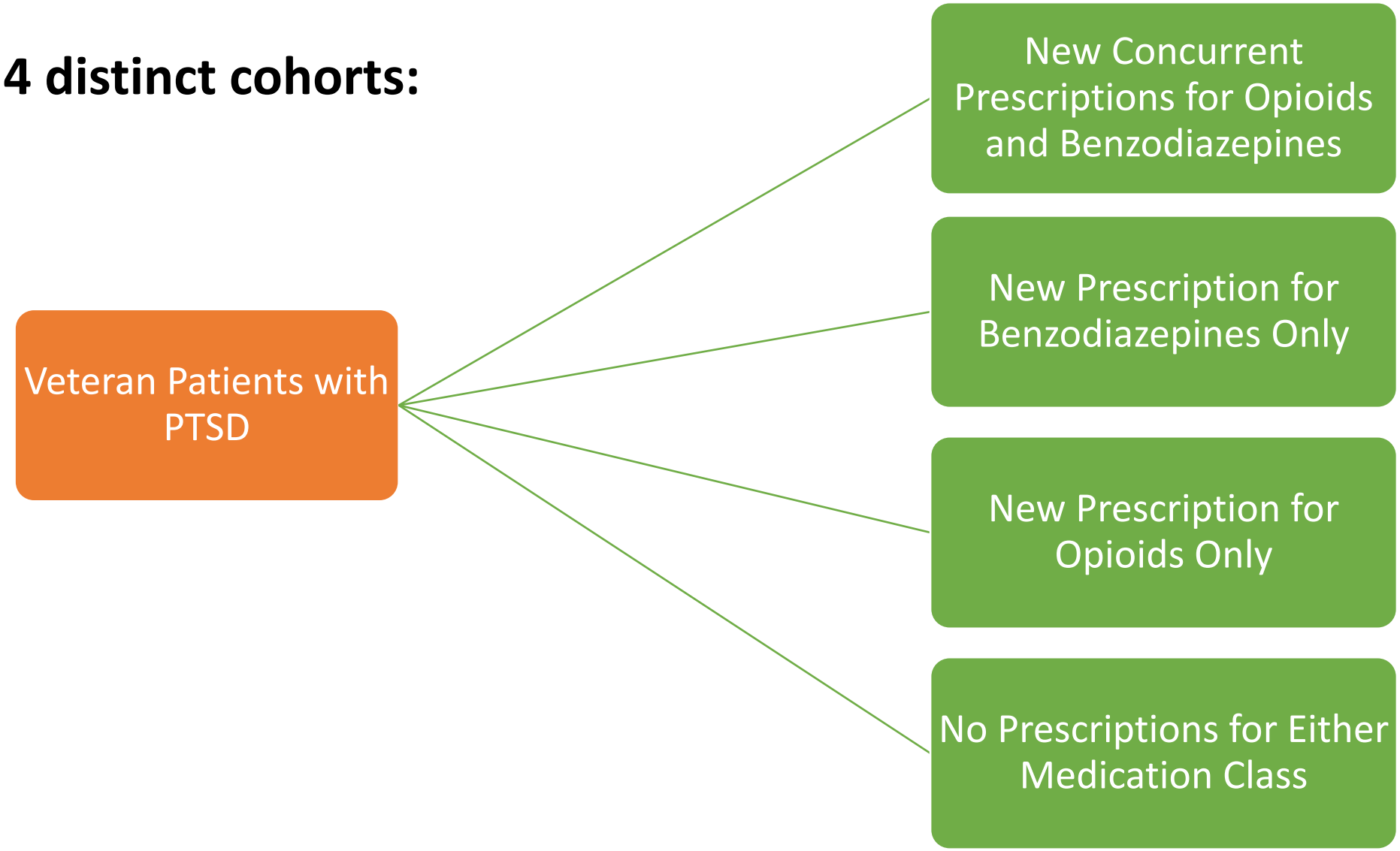
- Design
  - Propensity score-matched cohorts using retrospective data from 2010-2012
- Data Sources
  - Corporate Data Warehouse
    - Patient-level information on demographics, diagnoses, utilization and pharmacy data used to characterize cohorts and assess medication use
  - Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn Roster
    - Used to identify service, supplement missing race and ethnicity data
  - VA Vital Status Files
    - Used to ascertain death
  - VA/DoD Suicide Data Repository
    - Used to identify mortality cause

Sample

- Inclusion criteria
  - Veterans aged 18 or older
  - Primary or secondary diagnosis of PTSD documented at ≥1 outpatient visit(s) or inpatient discharge(s) from a VA facility in fiscal years 2010 - 2011
- Exclusion criteria
  - Documented cancer diagnoses or human immunodeficiency virus (HIV) in prior year
  - Receipt of hospice or opioid substitution treatment at any point in the study

Study Cohorts

- **Created 4 distinct cohorts:**



Cohort Definitions

New concurrent opioid and benzodiazepine therapies

- Received prescriptions for opioid and benzodiazepine medications within 30 days of each other
- Received medications concurrently for at least 30 consecutive days
- No more than 15-days cumulative supply of drugs from either medication class in the 6 months prior to study entry

New opioid-only therapy

- Received prescriptions for an opioid therapy for ≥30 consecutive days
- No more than 15-days cumulative supply of opioids in 6 months prior to study entry
- No use of benzodiazepine medications in the 6 months prior or 12 months following study entry

Cohorts Definitions Continued

New benzodiazepine-only therapy

- Received prescriptions for a benzodiazepine medication for ≥30 consecutive days
- No more than 15-days cumulative supply of benzodiazepines in 6 months prior to study entry
- No use of opioid medications in the 6 months prior or 12 months following study entry

Definition of non-users

- No prescriptions for either medication class in the 6 months prior or 12 months following study entry

Cohort Entry

- Concurrent medication users
  - Entered cohort on date prescriptions for opioids and benzodiazepines first overlapped
- Opioid-only (or Benzodiazepine-only)
  - Entered cohort release date of first opioid (or benzodiazepine) prescription
- Non-users
  - Identified first quarter in FY10-11 that patients attended ≥2 outpatient visits
  - First day of qualifying quarter was used as cohort entry date

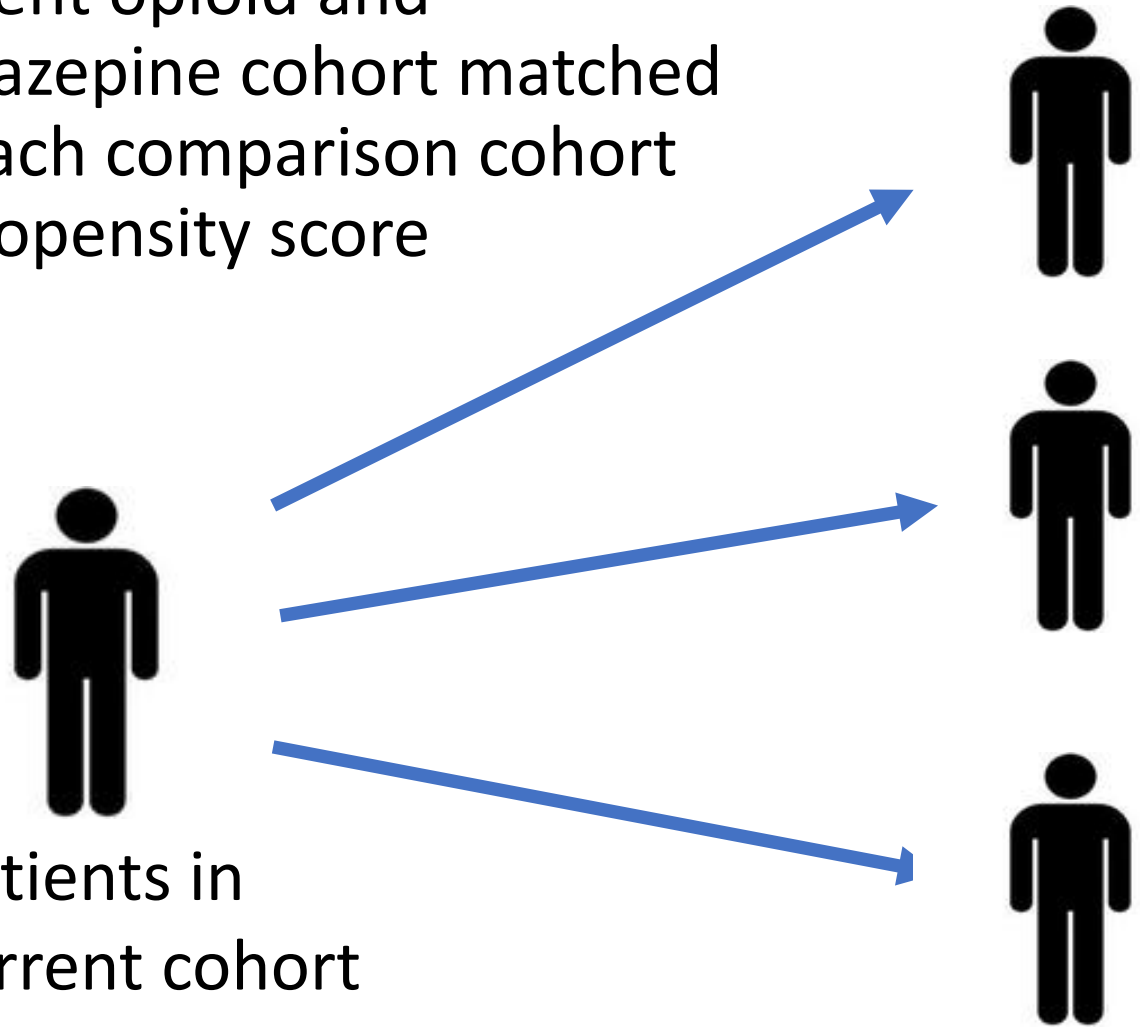
Propensity score models

- Derived from logistic regression models
  - Calculates the predicted propensity to receive to concurrent medication (vs. benzodiazepines only, opioids only, neither medication)
  - Corrects for observable differences between the cohort pairs
- Models included 41 covariates:
  - Demographics
  - Baseline mental health, substance use and medical diagnoses
  - Charlson Comorbidity Index
  - Baseline medication use (e.g. Z-Drugs, QT Prolongation Drugs)
  - Baseline treatment utilization
  - Initial opioid or benzodiazepine dose, as applicable
  - Facility-level complexity

Propensity-score matching

Parsons, Proceedings of the Twenty-Sixth Annual SAS Users Group International Conference; 2001.

- Concurrent opioid and benzodiazepine cohort matched 1:1 to each comparison cohort using propensity score



Follow-up and Endpoints

- Follow-up
  - Patients left the cohort one year after their entry date or on their date of death, whichever was earlier
  - Limited follow-up to one year to estimate short-term mortality risk
- Endpoints
  - Death by any cause, circulatory-related disease, respiratory-related disease and overdose during one-year follow-up

Analyses

Fine & Gray, Journal of the American Statistical Association; 1999.

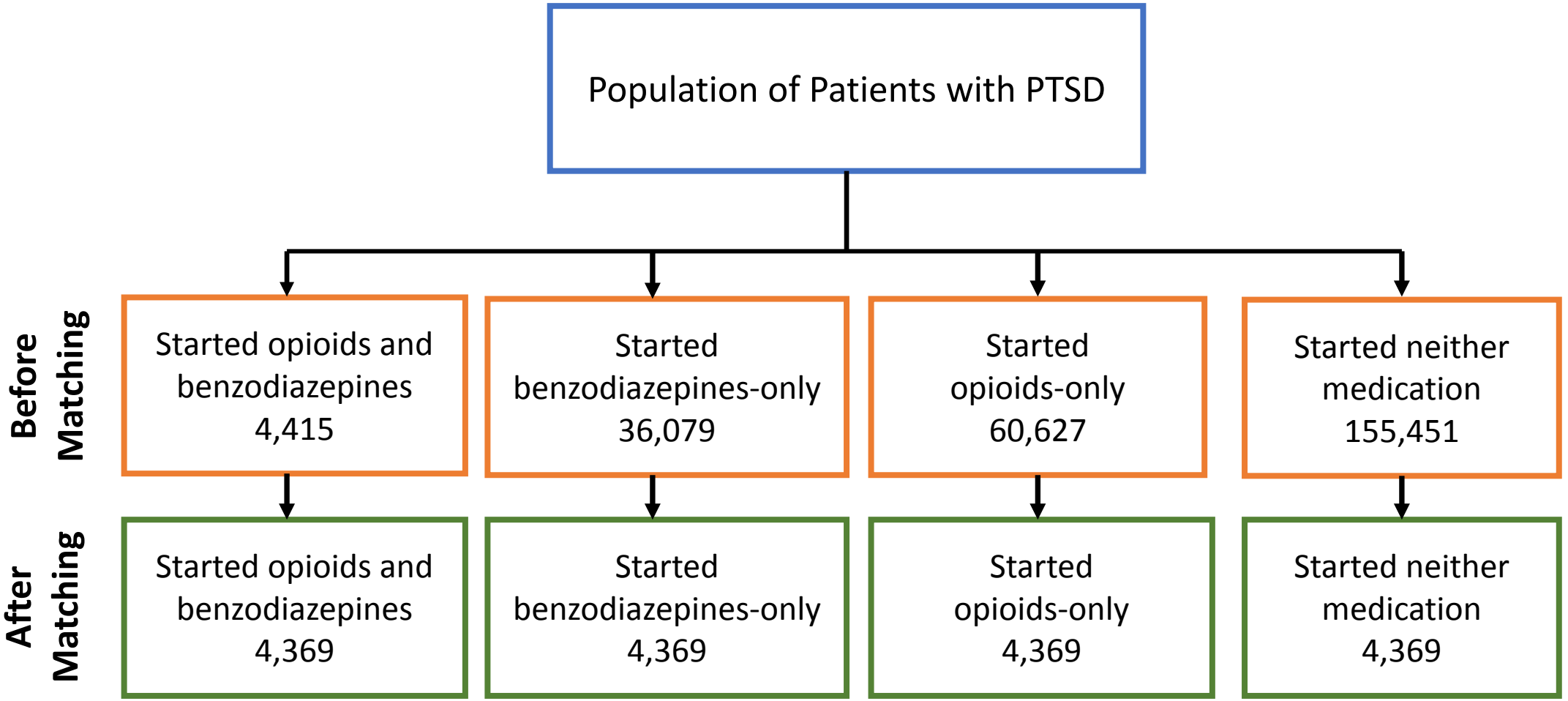
- All-cause mortality estimated from adjusted hazard ratios using Cox regression models
- Cause-specific mortality was estimated with adjusted subhazard ratios using Fine and Gray method
- Models adjusted for baseline propensity score, age, Charlson Co-morbidity Index (CCI) score, and count of mental health diagnoses, as well as covarying variable for daily dose of shared medication (if applicable)
    - Opioid and benzodiazepine doses were converted to morphine and diazepam milligram equivalents per day using standard conversions.

Sensitivity Analyses

- For all-cause mortality, sensitivity analyses were limited to patients:
  - Younger than 50 years old
  - With low medical comorbidity
    - Charlson Comorbidity Index = zero
  - With low(er) mental health comorbidity
    - PTSD only
  - Prescribed low opioid doses (<20 mg MEDD) and low benzodiazepine doses (<10 mg DEDD).

Results

Original and Matched Cohorts



Full Sample After Propensity Score Matching (n=17,746)

Characteristic	n (%)
Women	1,985 (11.4)
Age, year, M (SD)	47.1 (15.5)
OEF/OIF Veteran	6,220 (35.6)
Race	
Black	1,853 (10.6)
White	14,395 (82.4)
Other	844 (4.8)
Unknown	384 (2.2)
Psychiatric Conditions	
Anxiety Disorder	5,628 (32.2)
Bipolar Disorder	1,638 (9.4)
Psychotic Disorder	782 (4.5)
Depressive Disorder	8,689 (49.7)

Full Sample After Propensity Score Matching (n=17,746)

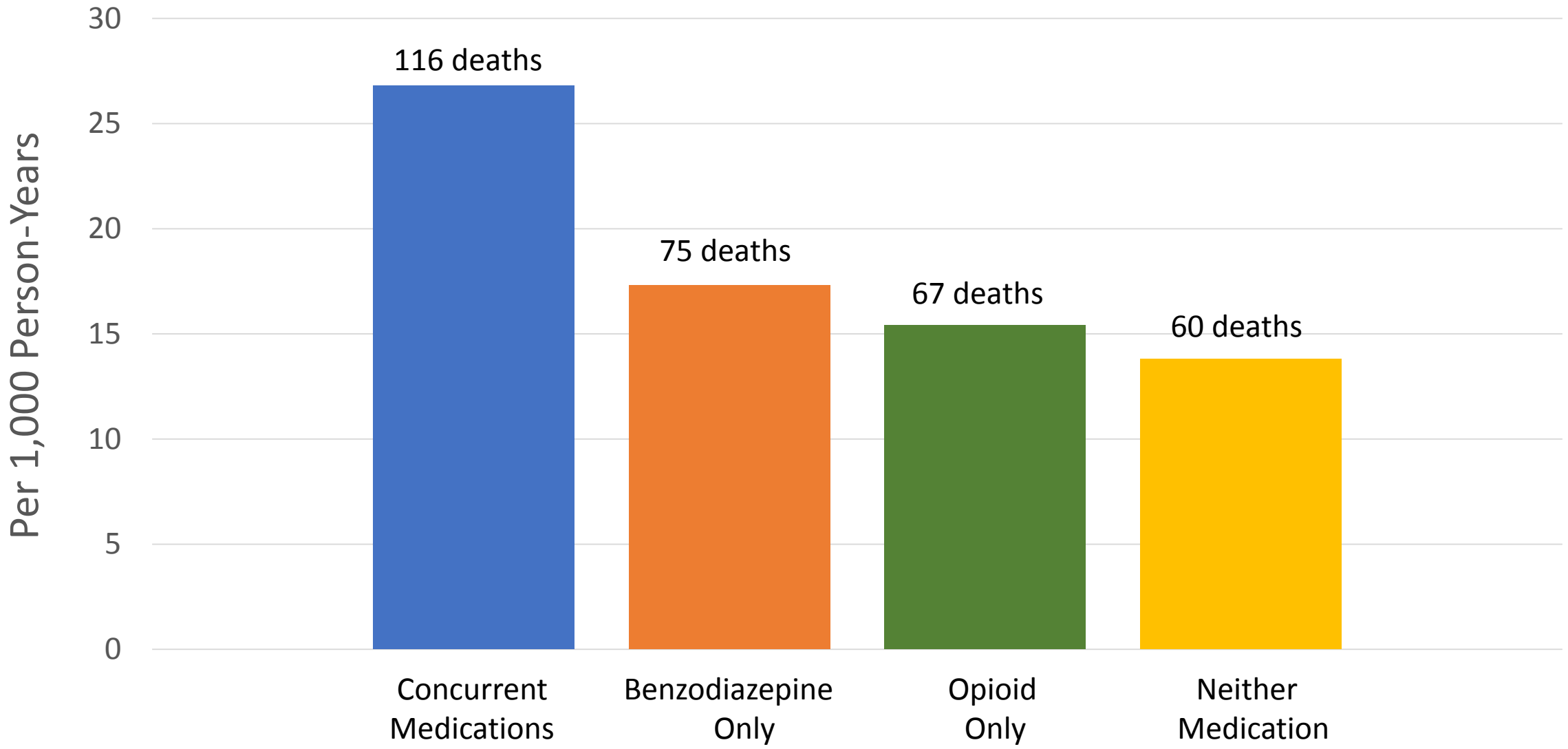
Characteristic	n (%)
Substance Use Conditions	
Alcohol Use Disorder	3,019 (17.3)
Opioid Use Disorder	516 (3.0)
Stimulant Use Disorder	732 (4.2)
Sedative Use Disorder	196 (1.1)
Cannabis Use Disorder	977 (5.6)
Use of Medications	
Z-drugs	3,222 (18.4)
QT prolongation-inducing	11,058 (63.3)
Medical Comorbidity	
Diabetes	2,583 (14.8)
Chronic Obstructive Pulmonary Disease	2,639 (15.1)
Pain Condition	14,893 (85.2)
Traumatic Brain Injury	1,470 (8.4)

Medication Doses by Cohort, Initial and 12-month Follow-up

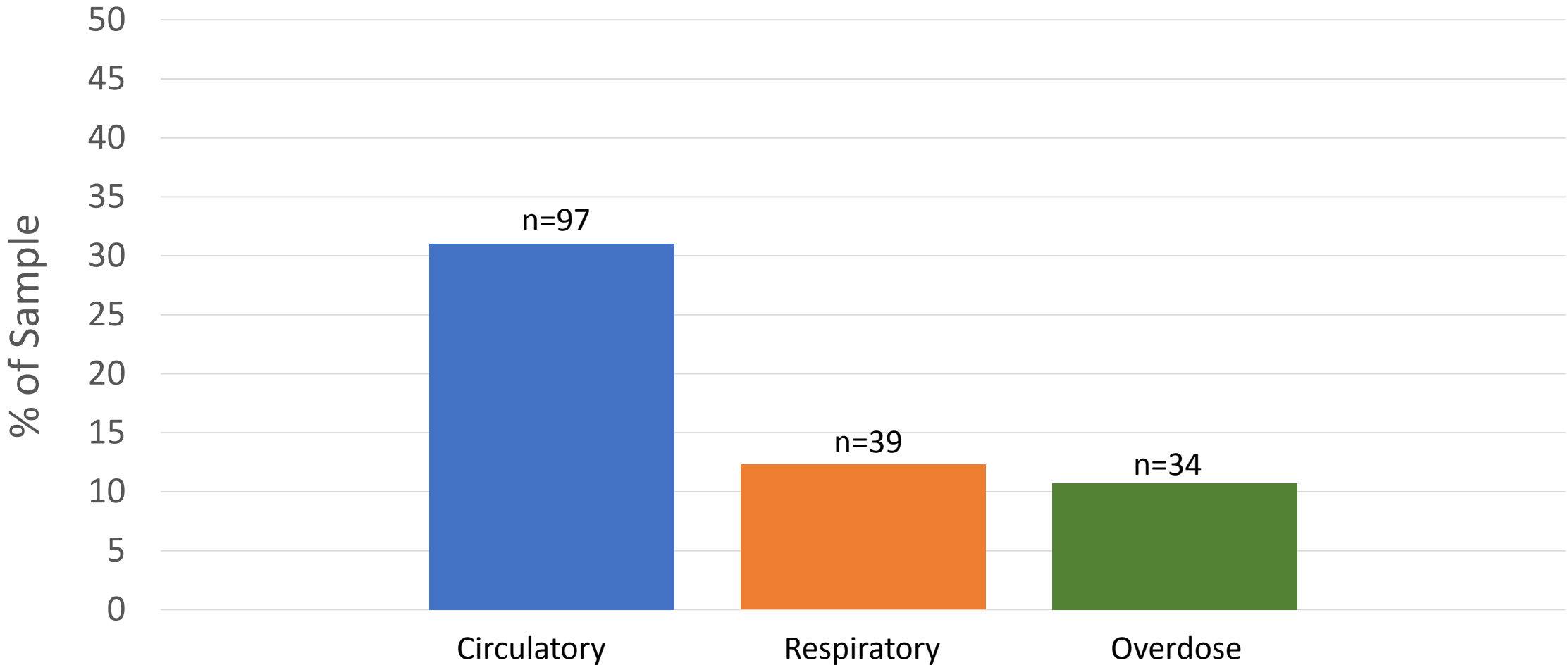
	Concurrent Opioids and Benzodiazepines (n = 4,369) M (SD)	Benzodiazepines Only (n = 4,369) M (SD)	p-value	Opioids Only (n = 4,369) M (SD)	p-value
Initial Daily Dose, mg					
Benzodiazepines, DEDD	21.0 (19.7)	20.5 (20.5)	0.183		
Opioids, MEDD	39.5 (56.0)			37.9 (63.7)	0.213
Daily Dose During Follow-up, mg					
Benzodiazepines, DEDD	22.9 (18.8)	21.1 (19.3)	<0.001		
Opioids, MEDD	42.7 (54.2)			37.7 (56.9)	<0.001

DEDD = diazepam milligram (mg) equivalents per day
MEDD = morphine mg equivalents per day

Total Deaths by Cohort



Common Causes of Death



Concurrent Medications vs. Benzodiazepines-Only

	Concurrent Medications		Benzodiazepines Only	
	Deaths, n	Incidence per 1,000 PY	Deaths, n	Incidence per 1,000 PY
All-cause mortality	116	26.8	75	17.3
Circulatory diseases	35	8.1	20	4.6
Respiratory diseases	14	3.2	9	2.1
Overdose	18	4.2	7	1.6

PY= Person-years

Concurrent Medications vs. Benzodiazepines-Only

	Concurrent Medications		Benzodiazepines Only				
	Deaths, n	Incidence per 1,000 PY	Deaths, n	Incidence per 1,000 PY	AHR/ASHR (95% CI)	ARD (95% CI)	p-value
All-cause mortality	116	26.8	75	17.3	1.52 (1.14, 2.03)	9.03 (2.43, 17.83)	0.004
Circulatory diseases	35	8.1	20	4.6	1.75 (0.94, 3.28)	3.48 (-0.28, 10.50)	0.078
Respiratory diseases	14	3.2	9	2.1	1.60 (0.77, 3.34)	1.26 (-0.48, 4.85)	0.206
Overdose	18	4.2	7	1.6	2.59 (1.00, 6.66)	2.56 (0.01, 9.15)	0.049

PY= Person-years; AHR=Adjusted hazard ratio; ASHR=Adjusted subhazard ratio; ARD=Adjusted risk difference
Analyses adjusted for propensity score, diazepam equivalents per day, age, CCI, count of mental health diagnoses

Concurrent Medications vs. Opioids-Only

	Concurrent Medications		Opioids Only	
	Deaths, n	Incidence per 1,000 PY	Deaths, n	Incidence per 1,000 PY
All-cause mortality	116	26.8	67	15.4
Circulatory diseases	35	8.1	23	5.3
Respiratory diseases	14	3.2	11	2.5
Overdose	18	4.2	7	1.6

PY= Person-years

Concurrent Medications vs. Opioids-Only

	Concurrent Medications		Opioids Only				
	Deaths, n	Incidence per 1,000 PY	Deaths, n	Incidence per 1,000 PY	AHR/ASHR (95% CI)	ARD (95% CI)	p-value
All-cause mortality	116	26.8	67	15.4	1.76 (1.32, 2.35)	11.74 (4.94, 20.81)	<0.001
Circulatory diseases	35	8.1	23	5.3	1.55 (0.89, 2.70)	2.90 (-0.59, 8.99)	0.123
Respiratory diseases	14	3.2	11	2.5	1.32 (0.65, 2.65)	0.80 (-0.88, 4.19)	0.443
Overdose	18	4.2	7	1.6	2.58 (1.09, 6.11)	2.54 (0.14, 8.23)	0.032

PY= Person-years; AHR=Adjusted hazard ratio; ASHR=Adjusted subhazard ratio; ARD=Adjusted risk difference
Analyses adjusted for propensity score, morphine equivalents per day, age, CCI, count of mental health diagnoses

Concurrent Medications vs. Neither Medication

	Concurrent Medications		Neither Medication	
	Deaths, n	Incidence per 1,000 PY	Deaths, n	Incidence per 1,000 PY
All-cause mortality	116	26.8	60	13.8
Circulatory diseases	35	8.1	19	4.4
Respiratory diseases	14	3.2	5	1.2
Overdose	18	4.2	2	0.5

PY= Person-years

Concurrent Medications vs. Neither Medication

	Concurrent Medications		Neither Medication				
	Deaths, n	Incidence per 1,000 PY	Deaths, n	Incidence per 1,000 PY	AHR/ASHR (95% CI)	ARD (95% CI)	p-value
All-cause mortality	116	26.8	60	13.8	1.85 (1.30, 2.64)	11.78 (4.10, 22.75)	0.001
Circulatory diseases	35	8.1	19	4.4	1.81 (1.01, 3.24)	3.54 (0.04, 9.80)	0.046
Respiratory diseases	14	3.2	5	1.2	2.79 (0.99, 7.82)	2.06 (-0.01, 7.87)	0.052
Overdose	18	4.2	2	0.5	9.16 (2.27, 37.02)	3.76 (0.58, 16.61)	0.002

PY= Person-years; AHR=Adjusted hazard ratio; ASHR=Adjusted subhazard ratio; ARD=Adjusted risk difference
Analyses adjusted for propensity score, age, CCI, count of mental health diagnoses

All-cause Mortality Sensitivity Analyses –
Concurrent Medications vs. Benzodiazepines Only

	Concurrent Medications		Benzodiazepines Only			
	Patients n	Deaths n (%)	Patients n	Deaths n (%)	AHR (95%CI)	p-value
Age <50 years	2,346	32 (1.4)	2,382	18 (0.8)	1.78 (1.01, 3.13)	0.046
Low Medical Comorbidity (Charlson Comorbidity Score = 0)	2,889	36 (1.2)	2,906	22 (0.8)	1.57 (0.97, 2.54)	0.068
Low Mental Health Comorbidity (PTSD Only)	1,325	35 (2.6)	1,320	19 (1.4)	1.81 (1.05, 3.13)	0.033
Low Dose (<10 mg DEDD, <20 mg MEDD)	349	13 (3.7)	1,085	18 (1.7)	2.30 (1.06, 4.99)	0.035

AHR=Adjusted hazard ratio
Analyses adjusted for propensity score and time-varying covariate for diazepam equivalents by day

All-cause Mortality Sensitivity Analyses –
Concurrent Medications vs. Opioids Only

	Concurrent Medications		Opioids Only			
	Patients n	Deaths n (%)	Patients n	Deaths n (%)	AHR (95%CI)	p-value
Age <50 years	2,346	32 (1.4)	2,308	13 (0.6)	2.33 (1.33, 4.09)	0.003
Low Medical Comorbidity (Charlson Comorbidity Score = 0)	2,889	36 (1.2)	2,845	21 (0.7)	1.65 (0.96, 2.82)	0.070
Low Mental Health Comorbidity (PTSD Only)	1,325	35 (2.6)	1,297	13 (1.0)	2.56 (1.37, 4.79)	0.003
Low Dose (<10 mg DEDD, <20 mg MEDD)	349	13 (3.7)	1,495	28 (1.9)	2.05 (0.98, 4.32)	0.058

AHR=Adjusted hazard ratio
Analyses adjusted for propensity score and time-varying covariate for morphine equivalents by day

All-cause Mortality Sensitivity Analyses –
Concurrent Medications vs. Neither Medication

	Concurrent Medications		Neither Medication			
	Patients n	Deaths n (%)	Patients n	Deaths n (%)	AHR (95%CI)	p-value
Age <50 years	2,346	32 (1.4)	2,359	3 (0.1)	10.78 (3.40, 34.17)	<0.001
Low Medical Comorbidity (Charlson Comorbidity Score = 0)	2,889	36 (1.3)	2,974	11 (0.4)	3.38 (1.76, 6.49)	<0.001
Low Mental Health Comorbidity (PTSD Only)	1,325	35 (2.6)	1,290	13 (1.0)	2.61 (1.38, 4.92)	0.003

AHR=Adjusted hazard ratio
Analyses adjusted for propensity score

Conclusions

- In year following first prescription, the likelihood of death among Veteran patients with PTSD who were co-prescribed benzodiazepines and opioids was:
  - 1.52 times greater than patients prescribed benzodiazepines only
  - 1.76 times greater than patients prescribed opioids only
  - 1.85 times greater than patients prescribed neither medication
- Corresponds to 9.0, 11.7, and 11.8 excess deaths per 1,000 person-years of new concurrent medication use relative to new use of benzodiazepines only, opioids only, and neither medication.
- Supports recommendations of Center for Disease Control and Prevention and VA/Department of Defense opioid therapy guidelines to:
  - avoid concurrent use of benzodiazepines and opioids
  - educate patients and prescribers about mortality risks of these medication classes, even when prescribed at low doses and among those with low comorbidity

Conclusions

- Risk of all-cause mortality similar in the 3 comparison cohorts
  - May reflect efforts to reduce confounding, which is common in observational research
  - Excluded patients with cancer diagnoses or HIV infection or in hospice or opioid substitution treatment to decrease potential confounding by indication
  - Rigorous matching – similar medical and mental health severity
    - Limited to patients with PTSD, matched according to propensity scores calculated from demographic, psychiatric and medical diagnoses, prescribed medications and service utilization variables possibly linked to mortality risk
  - Limited to new medication users to address survival bias and lessen possibility that long-term use of medications influenced results
  - Adjusted for daily dose of shared medication – lessens the possibility that high doses are influencing the results
  - Sensitivity analyses test robustness of primary findings and study assumptions among younger patients, those with low medical and mental health comorbidity, and those receiving low doses of both opioids and benzodiazepines.

Conclusions

- Patients receiving opioid and benzodiazepine medications were nearly 3 times as likely to die by overdose than those prescribed either medication class alone
- Nearly 90% of deaths were due to non-overdose causes
  - Circulatory diseases accounted for 31% of total deaths
  - Concurrent users at increased risk of circulatory disease, relative to non-user cohort
    - highlights potential risk for clinicians to consider
  - No differences detected in deaths due to respiratory-related causes in any cohort or in circulatory-related causes in benzodiazepine-only and opioid-only cohorts
    - Point estimates do indicate increased risk, may not be powered to detect differences
- Findings were similar and most remained significant in sensitivity analyses
  - younger patients
  - low mental health comorbidity
  - low doses of both opioids (< 20 mg MEDD) and benzodiazepines (<10 mg DEDD) (relative to benzodiazepine-only cohort)
  - Low medical comorbidity (relative to neither medication cohort only)

Limitations

- A focus on single mental health condition limits generalizability of results
- Differences on unmeasured variables (e.g., PTSD and pain severity) may have impacted study results
- Prescription data reflect outpatient fills only and do not account for medications received in community or capture medication compliance
- Study cohorts may differ from typical population of patients receiving these medications
- Analyses did not account for whether patients were receiving mediations at the time of death
- Analyses of disease-specific causes of death and sensitivity analyses may be underpowered
- Patients in each of the three comparison cohorts were matched separately to patients in the concurrent medication cohort, comparisons between opioid-only, benzodiazepine-only and non-user medication cohorts were not possible.

Implications

Malte et al., Medical Care, 2018; Jamtvedt et al., Cochrane Database Syst Rev, 2006; Scascighini et al., Rheumatology, 2008; Kamper et al., Cochrane Database Syst Rev, 2014.

- Strategies to prevent co-prescribing and promote safe discontinuation/tapering among those at risk are needed
  - Traditional education approaches - passive dissemination of materials, educational meetings in isolation - are minimally effective as risk mitigation strategies
  - Multifaceted interventions including medication alerts or reminders, audit and feedback appear promising in reducing co-prescribing
  - Involvement of both primary care and mental health prescribers critical given that these medication classes are often prescribed in different settings
  - Patients with significant physical and psychosocial impairments from pain conditions may require multidisciplinary pain care to support discontinuation/tapering one or both of these medications

Questions or Comments?

Contact Information

Eric Hawkins: eric.hawkins@va.gov

Carol Malte: carol.malte@va.gov

References/Helpful Resources

- VA/DoD Clinical Practice Guidelines: https://www.healthquality.va.gov/
- CDC Guideline for Prescribing Opioids for Chronic Pain: https://www.cdc.gov/drugoverdose/prescribing/guideline.html
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Oral Opioid and Benzodiazepine Medications Included in the Study

Opioid Medications	Benzodiazepine Medications
codeine	alprazolam
morphine	chlordiazepoxide
oxycodone	clonazepam
hydrocodone	clorazepate
oxymorphone	diazepam
propoxephene	flurazepam
hydromorphone	lorazepam
levorphanol	oxazepam
meperidine	temazepam
methadone*	triazolam
tramadol	
pentazocine	
fentanyl[1]	
butorphanol[2]	

Note: * = tablets only to exclude unit dosing received in opioid use disorder treatment programs.

[1] includes transdermal fentanyl

[2] nasal spray

Patient Characteristics in Original and Matched Cohorts

		Original Samples			
	Final Sample n=17,476 n (%)	Concurrent n=4,415 n (%)	Benzodiazepine Only n=36,079 n (%)	Opioid Only n=60,627 n (%)	No Medication n=155,451 n (%)
Age, M (SD)	47.1 (15.5)	47.3 (15.1)	51.2 (16.2)	53.1 (14.7)	51.6 (16.7)
Women	1,985 (11.4)	506 (11.5)	3,742 (10.4)	4,184 (6.9)	9,751 (6.3)
Race					
Black	1,853 (10.6)	471 (10.7)	4,537 (12.6)	15,047 (24.8)	29,941 (19.3)
White	14,395 (82.4)	3,629 (82.2)	27,194 (75.4)	40,512 (66.8)	111,132 (71.5)
Other	844 (4.8)	213 (4.8)	1,698 (4.7)	3,374 (5.6)	8,278 (5.3)
Unknown	384 (2.2)	102 (2.3)	2,650 (7.3)	1,694 (2.8)	6,100 (3.9)
Service Era					
OEF/OIF	6,220 (35.6)	1,544 (35.0)	11,200 (31.0)	15,002 (24.7)	50,715 (32.6)
Psychiatric Conditions					
Anxiety Disorder	5,628 (32.2)	1,445 (32.7)	11,083 (30.7)	8,936 (14.7)	20,974 (13.5)
Bipolar Disorder	1,638 (9.4)	407 (9.2)	2,611 (7.2)	2,883 (4.8)	4,918 (3.2)
Psychotic Disorder	782 (4.5)	199 (4.5)	1,505 (4.2)	2,243 (3.7)	4,275 (2.8)
Depressive Disorder	8,689 (49.7)	2,181 (49.4)	18,400 (51.0)	29,336 (48.4)	61,721 (39.7)

Patient Characteristics in Original and Matched Cohorts

			Original Samples		
	Final Sample n=17,476 n (%)	Concurrent n=4,415 n (%)	Benzodiazepine Only n=36,079 n (%)	Opioid Only n=60,627 n (%)	No Medication n=155,451 n (%)
Substance Use Conditions					
Alcohol Use Disorder	3,019 (17.3)	755 (17.1)	5,604 (15.5)	12,375 (20.4)	26,057 (16.8)
Opioid Use Disorder	516 (3.0)	146 (3.3)	419 (1.2)	1,104 (1.8)	1,170 (0.8)
Stimulant Use Disorder	732 (4.2)	191 (4.3)	810 (2.3)	3,729 (6.2)	3,998 (2.6)
Sedative Use Disorder	196 (1.1)	55 (1.3)	176 (0.5)	218 (0.4)	219 (0.1)
Medical Comorbidity					
Diabetes	2,583 (14.8)	668 (15.1)	6,111 (16.9)	14,733 (24.3)	25,873 (16.6)
COPD	2,639 (15.1)	679 (15.4)	4,039 (11.2)	9,697 (16.0)	13,698 (8.8)
Pain	14,893 (85.2)	4,449 (85.6)	23,957 (47.8)	67,188 (89.1)	100,180 (49.0)
Traumatic Brain Injury	1,470 (8.4)	361 (8.2)	1,516 (4.2)	2,992 (4.9)	5,035 (3.2)
Medications					
Z-Drugs	3,222 (18.4)	838 (19.0)	6,293 (17.4)	7,481 (12.3)	10,516 (6.8)
QT Drugs	11,058 (63.3)	2,797 (63.4)	21,680 (60.1)	38,174 (63.0)	63,789 (41.0)

Days of Medication and Average Dose by Cohort

		Concurrent Medications n (%)	Benzodiazepine Only n (%)	Opioid Only n (%)
Benzodiazepines				
Days of Use	<90	1169 (26.8)	1680 (38.5)	
	90 - 179	1056 (24.2)	1218 (27.9)	
	≥180	2144 (49.1)	1471 (33.7)	
Average Dose	<10	908 (20.8)	1085 (24.8)	
	10-39	2670 (61.1)	2687 (61.5)	
	≥40	791 (18.1)	597 (13.7)	
Opioids				
Days of Use	<90	1,170 (26.8)		1973 (45.2)
	90 - 179	992 (22.7)		1082 (24.8)
	≥180	2,207 (50.5)		1314 (30.1)
Average Dose	<20	1,224 (28.0)		1495 (34.2)
	20-49	2,190 (50.1)		2206 (50.5)
	≥50-99	652 (14.9)		491 (11.2)
	≥100	303 (6.9)		177 (4.1)