

Dual Use of Controlled Substances in and outside of VA: Clinical Context and Measurement Challenges

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Pain Research, Informatics, Multimorbidities, and Education

Enhancing Pain Care for Veterans



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Learning objectives

- Describe the current landscape of opioid safety efforts in VA
- Understand methods for measuring prescription opioid exposure
- Understand better the patterns of dual use (VA/non-VA) of opioids through lessons learned from a project among Kentucky Veterans

Polling Question 1 for Audience

Your role in VA (select all that apply)

Clinician

Pain researcher

Substance use researcher

Other researcher

Data scientist/analyst

Outline

- Long-term opioid therapy for chronic pain:
 - Why VA is pulling back
 - How VA is pulling back
 - Evidence that pull-back is working
 - Evidence that overdoses continue to climb
- Measuring opioid exposure in pharmacoepidemiologic research
- Our work examining dual use of opioids/risky prescribing

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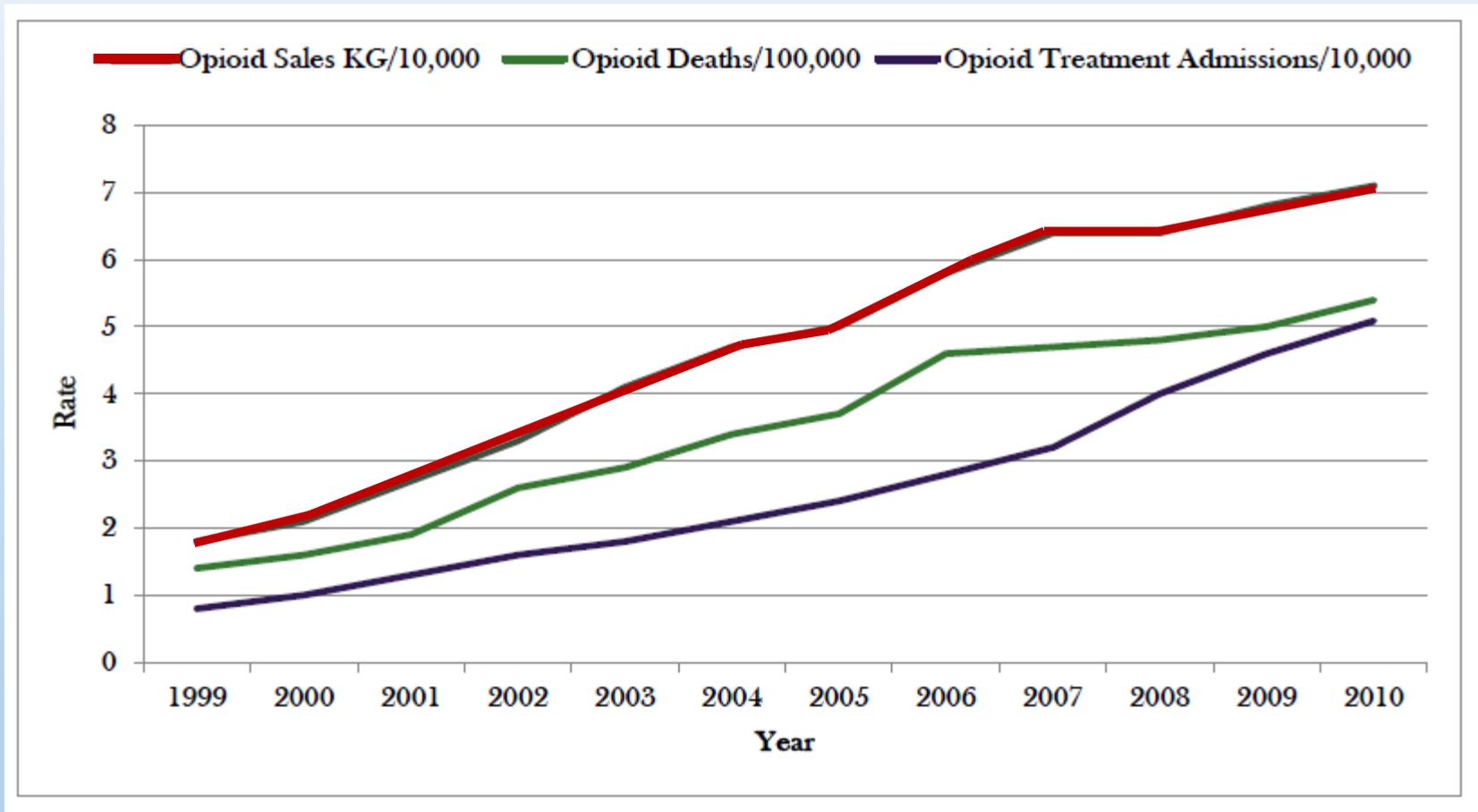
Polling Question 2 for Audience

Do you prescribe opioids?

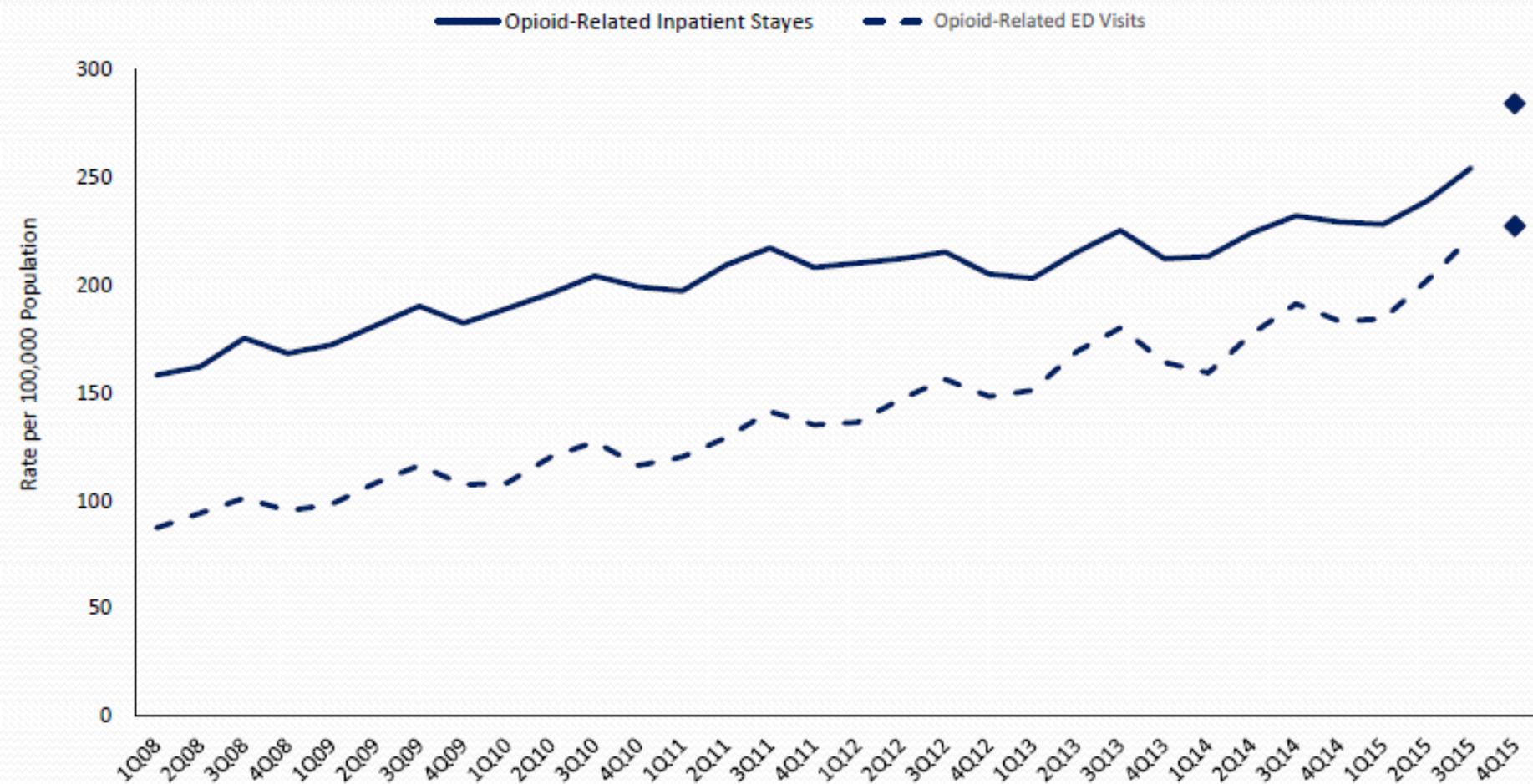
Yes

No

Trends in prescribing and harm



Opioid-related hospitalizations and ED visits, 2008-2015



Source: AHRQ HCUP



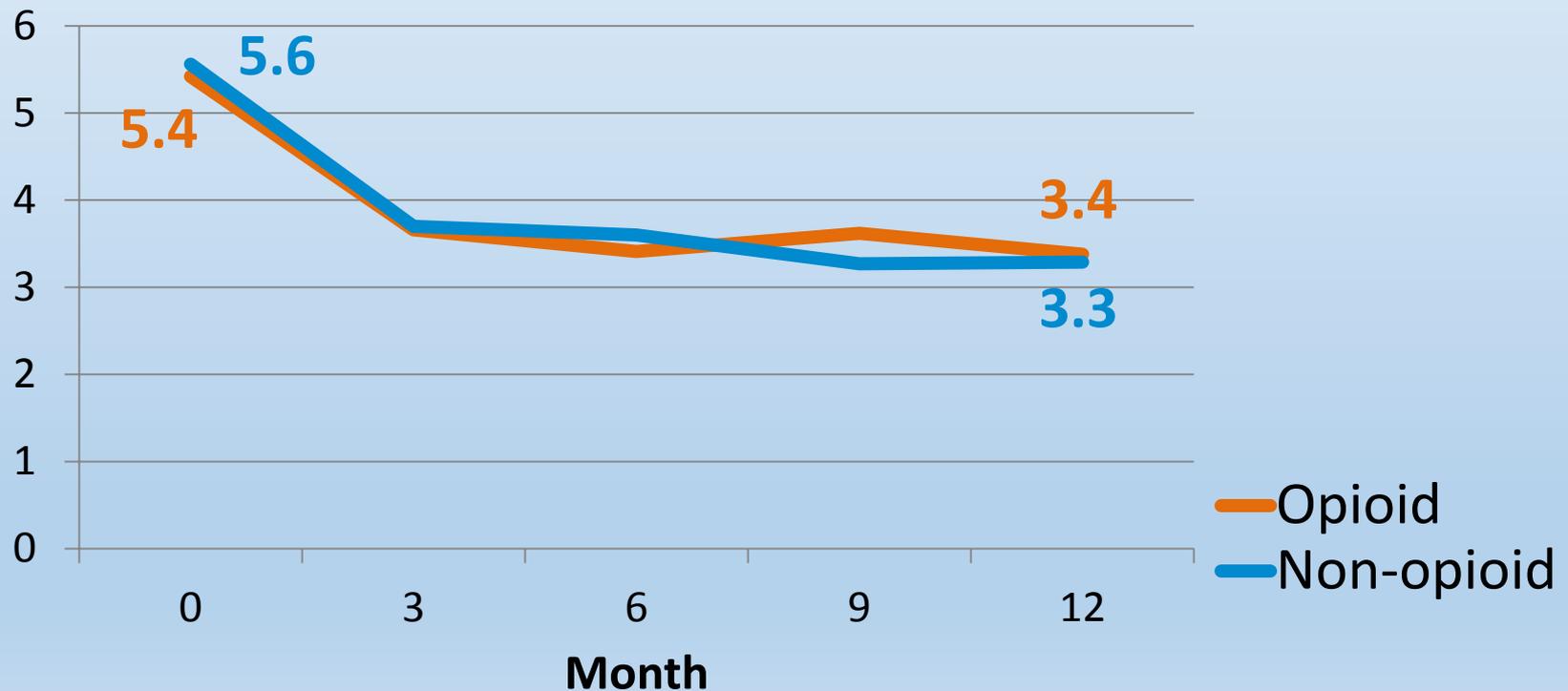
CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016

- “[N]o study of opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for chronic pain evaluated long-term (≥ 1 year) outcomes related to pain, function, or quality of life. Most placebo-controlled randomized clinical trials were ≤ 6 weeks in duration.”

Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain

The SPACE Randomized Clinical Trial

Mean BPI Interference (n=238)

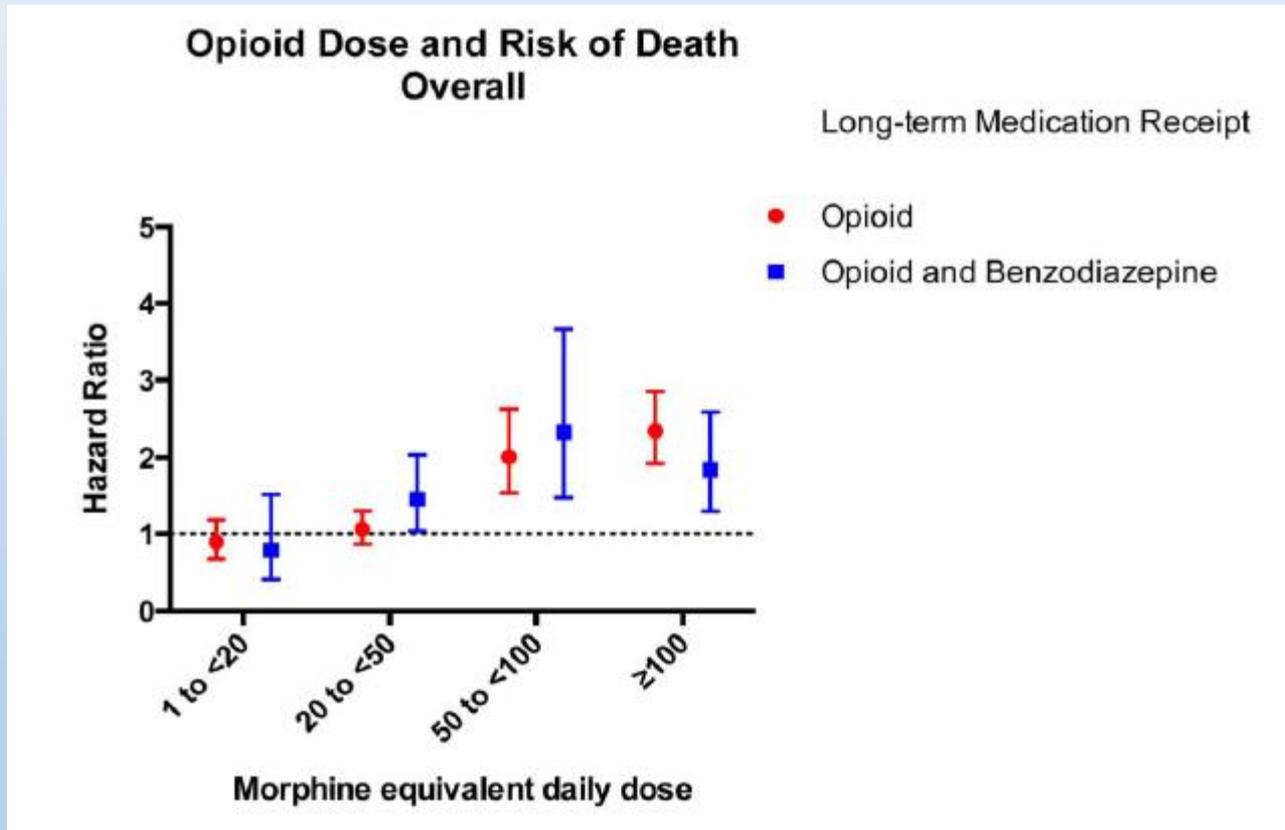


Direct association between prescribed dose and overdose

Dose* (mg/day)	HR (95% CI)
1-<20	1.00 (REF)
20-<50	1.9 (1.3-2.7)
50-<100	4.6 (3.2-6.7)
≥100	7.2 (4.9-10.7)

*morphine equivalent

Co-prescribed benzodiazepines



VA/DoD CLINICAL PRACTICE GUIDELINE FOR OPIOID THERAPY FOR CHRONIC PAIN

#	Recommendation	Strength*	Category†
Initiation and Continuation of Opioids			
1.	<ul style="list-style-type: none"> a) We recommend against initiation of long-term opioid therapy for chronic pain. b) We recommend alternatives to opioid therapy such as self-management strategies and other non-pharmacological treatments. c) When pharmacologic therapies are used, we recommend non-opioids over opioids. 	<ul style="list-style-type: none"> a) Strong against b) Strong for c) Strong for 	Reviewed, New-replaced
2.	<p>If prescribing opioid therapy for patients with chronic pain, we recommend a short duration.</p> <p>Note: Consideration of opioid therapy beyond 90 days requires re-evaluation and discussion with patient of risks and benefits.</p>	Strong for	Reviewed, New-added
3.	For patients currently on long-term opioid therapy, we recommend ongoing risk mitigation strategies (see Recommendations 7-9), assessment for opioid use disorder, and consideration for tapering when risks exceed benefits (see Recommendation 14).	Strong for	Reviewed, New-replaced

Other Opioid Safety Initiative-related safety steps

- Routine urine drug monitoring
- Routine PDMP querying
- Availability of non-pharmacologic treatment options for pain
- Availability of medication-assisted treatment for opioid use disorder

Polling Question 3 for Audience

Have you accessed/used an opioid safety dashboard?

Often

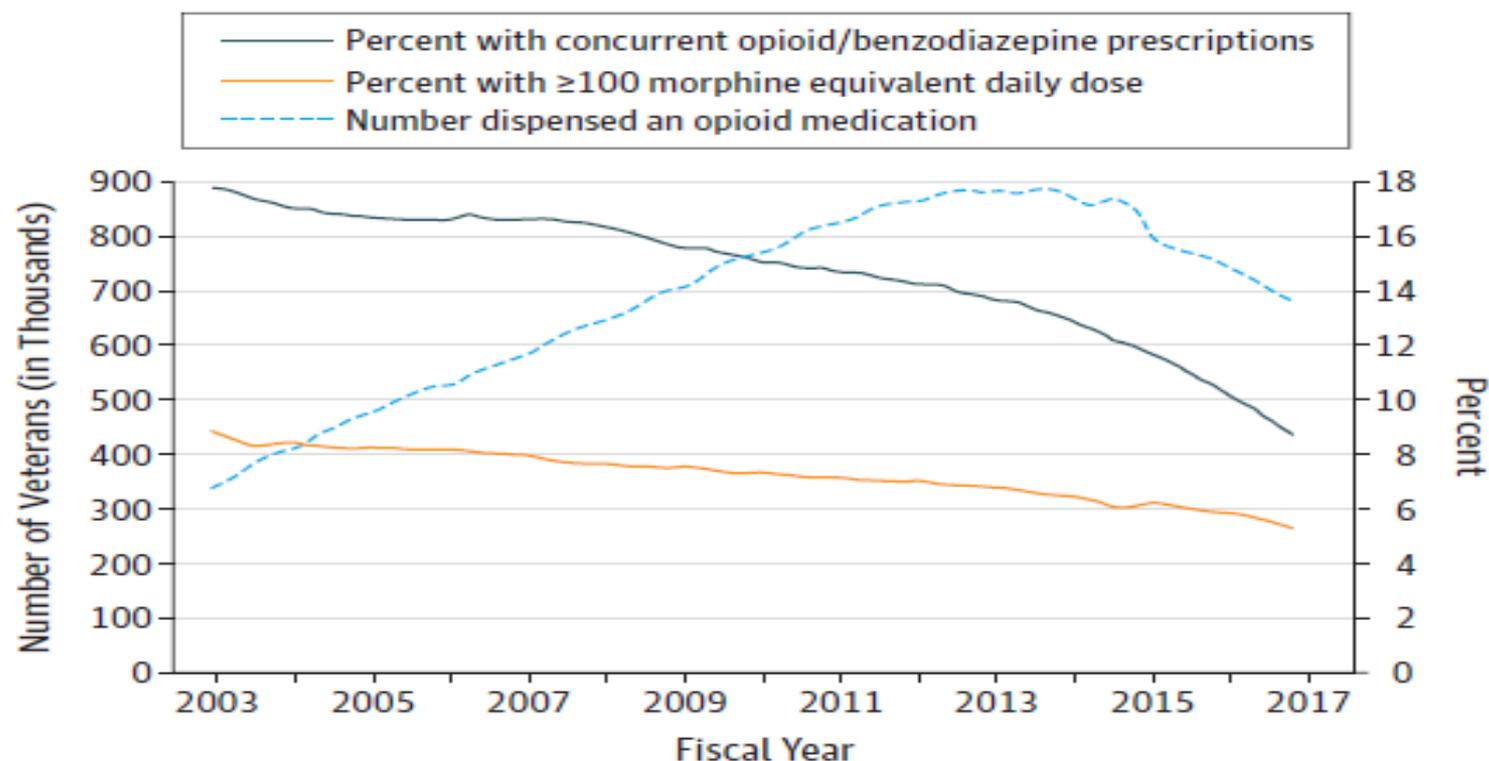
Sometimes

Rarely

Never

VA has seen declines in risky prescribing

Figure. Veterans Dispensed at Least 1 Opioid Medication in the VA Health Care System and Percent of Opioid Recipients With Concurrent Benzodiazepine Prescriptions and High Opioid Dosage



Data are from VA Pharmacy Benefits Management Services and presented by quarter, fiscal years 2003 through 2016.

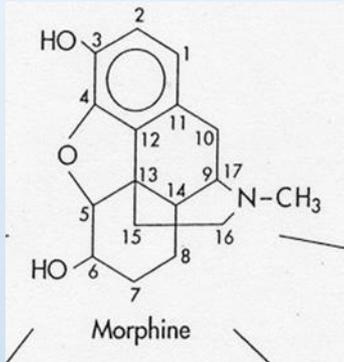
Multi-factorial explanation

- Transition to other opioids:
 - Non-VA prescribed pills
 - Non prescribed pills, cheaper, more potent heroin or high potency fentanyl and its analogues
 - Higher rate of OD, esp. among individuals not expecting fentanyl to be there
 - Higher rate of death among individuals who OD
- Substitution with other agents: alcohol, bzds
- Lag time of epidemic: victims now are experiencing consequences of prescribing patterns from ten years ago
- Access to medication-assisted treatment for opioid use disorder not keeping up with demand
- Access to naloxone not keeping up with demand

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Opioid analgesics (opiates + opioids)

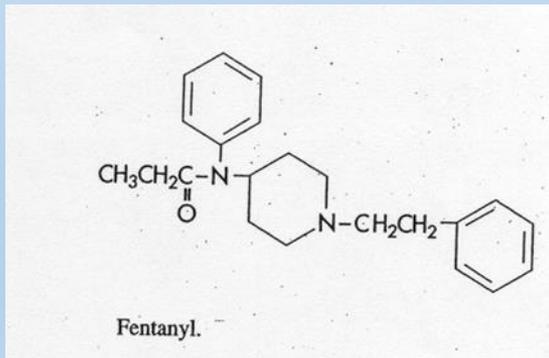


Opiates

- Naturally present in opium from seedpod of *Papaver somniferum*
- Morphine, codeine
- Addition of 2 acetyl groups: heroin

Opioids

- Manufactured
- Semi-synthetics: oxycodone hydrocodone, hydromorphone
- Synthetics: fentanyl, methadone, buprenorphine



Medication-assisted therapy for opioid use disorder

- Methadone – liquid form, dispensed by federally regulated Opiate Treatment Programs -- **not** listed in PBM/VINCI files
 - Buprenorphine – sublingual tablet or film -- **is** listed in PBM/VINCI files
 - Naltrexone – intramuscular injection -- **is** listed in PBM/VINCI
-

- Buprenorphine patch (Butrans) exclusively used for pain
- Sublingual buprenorphine “off label” for pain is rare in VA
- Methadone for OUD and methadone for pain can be reliably distinguished by their formulation and who is holding the data



Sources of opioid exposure grid

Indication	Within VHA		Outside VHA		Non Healthcare
	Outpatient	Inpatient	Outpatient	Inpatient	
Pain					
Opioid Use Disorder					
Illicit					

Sources measured depends on research question

Indication	Within VA		Outside VA		Non Healthcare
	Outpatient	Inpatient	Outpatient	Inpatient	
Pain					
Opioid Use Disorder					
Illicit					

Does having access to outside prescribers lead to riskier outpatient opioid regimens for pain?

Indication	Within VA		Outside VA		Non Healthcare
	Outpatient	Inpatient	Outpatient	Inpatient	
Pain	Green	White	Green	White	Dark Gray
Opioid Use Disorder	Light Blue	Light Blue	Light Blue	Light Blue	Dark Gray
Illicit	Dark Gray	Dark Gray	Dark Gray	Dark Gray	White

Does cumulative opioid exposure among oft-hospitalized older patients lead to premature death?

Indication	Within VA		Outside VA		Non Healthcare
	Outpatient	Inpatient	Outpatient	Inpatient	
Pain					
Opioid Use Disorder					
Illicit					

What additional opioid exposure is contributing to rising overdose rates?

Indication	Within VA		Outside VA		Non Healthcare
	Outpatient	Inpatient	Outpatient	Inpatient	
Pain					
Opioid Use Disorder					
Illicit					

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	Outpatient	Inpatient	Outpatient	Inpatient	
Pain	Green	White	Green	White	Dark Gray
Opioid Use Disorder	Light Blue	Light Blue	Light Blue	Light Blue	Dark Gray
Illicit	Dark Gray	Dark Gray	Dark Gray	Dark Gray	White

Morphine equivalent dose

- Method of standardizing potency across various opioid compounds
- Based on equianalgesic tables from dose ranging studies
- Example:
20 mg oxycodone TID
=
90 mg morphine
equivalent daily dose

Calculating morphine milligram equivalents (MME)

OPIOID (doses in mg/day except where noted)	CONVERSION FACTOR
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
≥ 61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

These dose conversions are estimated and cannot account for all individual differences in genetics and pharmacokinetics.

Assign a per-day dose to each individual in the sample

- Each individual prescription has:
 - Start date
 - Medication and strength
 - Number of pills and directions
 - Days' supplied → end date
- E.g. Morphine sustained release 30 mg tab, take one tab three times a day for 28 days. 84 pills prescribed.
 - For that 28-day period, mg morphine equivalent daily dose = 90.
- Over same 28-day period: oxycodone IR 10 mg tab, take one tab four times a day as needed. 112 pills prescribed.
 - Additional 40 mg/day oxycodone = 60 mg MEDD.
 - Total MEDD = 150 mg

Denominator is important

- Over four months, patient receives three 30-day prescriptions for morphine immediate release 15 mg three times/day (90 pills). These prescriptions were interrupted by two 15-day hospitalizations.



- For that 120 day period: total mg morphine taken = $45 \times 90 = 4050$
 - Average exposure over time period = $4050/120 = 33.75$ mg/day
 - Average daily *dose* = $4050/90 = 45$ mg MEDD
- Convention is to only calculate *dose* for days medication is supplied
- There still may be good reasons to calculate average exposure over a period of time

Outpatient pain prescribing

INCLUDED	EXCLUDED
<ul style="list-style-type: none">•Outpatient Prescriptions	<ul style="list-style-type: none">•Inpatient Prescriptions
<ul style="list-style-type: none">•Oral•Transdermal	<ul style="list-style-type: none">•Infrequently Used Preparations<ul style="list-style-type: none">•Rectal suppositories•Crystals•Powders•Films•Injection
<ul style="list-style-type: none">•Codeine; fentanyl; hydrocodone; hydromorphone; methadone; morphine, morphine (SA); oxycodone, oxycodone (SA); propoxyphene; and tramadol	<ul style="list-style-type: none">•Opioid Agonist Treatment<ul style="list-style-type: none">•Buprenorphine•Methadone for MMT

- Standard conversion factors to determine morphine equivalent dose of each prescription

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VA & Non-VA prescriptions

Prescription Drug Monitoring Programs

- Every prescription for > 72-hour supply of a controlled substance must be put in the PDMP/PMP, associated with the individual medical provider's DEA number
- Each state has one, some agreements allow providers to look across multiple states
- VA facilities share prescription data with their state PDMP
- Safety: Providers to check individual patient prescription past and current history of controlled substances before prescribing

'Big picture' available from PDMP data

Aggregate data to determine what's happening across:

- Geographic areas
 - States or region(s) within a given state
- Time
 - With or without policy changes
- Health providers
 - Use of queries in PDMP, prescriptions dispensed

Project objective

To determine whether out-of-system access to controlled substance prescribers is associated with ***risky opioid therapy*** among Veterans, adjusting for key demographic and *clinical characteristics*

2016 CDC Guideline for Prescribing Opioids for Chronic Pain

- Also part of VA guidelines
- “...and should avoid increasing dosage to ≥ 90 MME/day”
- “Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible”

Methods – I.

- Design: Prospective cohort study
- Sample: Kentucky-residing Veterans who enrolled in the Choice program and matched controls not enrolled
 - CHOICE Enrollees: Non-enrollees (1:4 ratio)
 - Matching factors: sex, age (+/- 5 years), race/ethnicity

Methods – II.

- Data source: Kentucky All Schedule Prescription Electronic Reporting (KASPER) system
- Time: 18 month period
- Covariates – Demographic & clinical factors, prescriber in/outside VA
- Outcomes: Risky prescribing indicators: 1- High dose opioids; 2- Combination of opioids and benzodiazepines (at least 1 day overlap)

Overlap & Adding up Prescriptions

- Use a “medicine cabinet supply” approach
- Take each prescription available to a patient (dispensed) and calculate the number of days each one will last.
- On days where there is more than one prescription available to a patient:
 - For opioids, their morphine equivalents are added together
 - For benzodiazepines, opioids are considered to be delivered in combination if there is even one day of overlap of the prescriptions, regardless of dose

Opioids and Risky Prescribing Indicators

Any opioid prescription	50.3%	36.7%	p<.0001
High-dose	3.3%	2.3%	p<.0001
Opioid-benzo combo	7.9%	4.7%	p<.0001

High-Dose Opioids

Logistic Regression N=44,635	Odds Ratio (95% CI)
Female	0.95 (0.77, 1.16)
36-54	2.16 (1.53, 3.05)
55-64	2.79 (1.99, 3.92)
65+	1.77 (1.26, 2.49)
Black	0.55 (0.44, 0.71)
Hispanic	0.31 (0.10, 0.96)
Other	1.16 (0.92, 1.47)
Choice status – Yes	1.33 (1.16, 1.53)
Cancer diagnosis	2.01 (1.72, 2.35)
Opioid use disorder	5.09 (3.83, 6.78)
Drug use dx (not opioids, tobacco)	0.56 (0.39, 0.80)
Alcohol use disorder	0.77 (0.60, 0.99)
PTSD	1.17 (0.98, 1.40)
Depression	1.30 (1.10, 1.54)
Bipolar	0.80 (0.60, 1.07)
Schizophrenia	0.12 (0.02, 0.87)

Opioid-Benzodiazepine Combination

Logistic Regression N=44,635	
Female	
36-54	
55-64	
65+	
Black	
Hispanic	
Other	
Choice status – Yes	
Cancer diagnosis	1.68 (1.50, 1.88)
Opioid use disorder	
Drug use dx (not opioids, tobacco)	
Alcohol use disorder	
PTSD	
Depression	
Bipolar	
Schizophrenia	

High-Dose Opioids: Opioid Subsample

Logistic Regression N=17,601	Odds Ratio (95% CI)
Female	0.92 (0.74, 1.14)
36-54	1.63 (1.15, 2.31)
55-64	1.91 (1.35, 2.70)
65+	1.31 (0.93, 1.86)
Black	0.55 (0.43, 0.70)
Hispanic	0.47 (0.15, 1.50)
Other	1.29 (1.01, 1.65)
Choice status – Yes	1.00 (0.87, 1.15)
Non VA prescriber	2.16 (1.85, 2.53)
Cancer diagnosis	1.63 (1.39, 1.91)
Opioid use disorder	3.31 (2.49, 4.40)
Drug use disorder (not opioids, tobacco)	0.60(0.42, 0.85)
Alcohol use disorder	0.82 (0.64, 1.06)
PTSD	1.09 (0.91, 1.31)
Depression	1.05 (0.89, 1.24)
Bipolar	0.76 (0.57, 1.01)
Schizophrenia	0.19 (0.03, 1.39)

Opioid-Benzo Combo: Opioid Subsample

Logistic Regression N=17,601	Odds Ratio (95% CI)
Female	1.11 (0.95, 1.29)
36-54	1.91 (1.46, 2.50)
55-64	3.12 (2.39, 4.08)
65+	2.67 (2.05, 3.49)
Black	0.48 (0.40, 0.57)
Hispanic	0.36 (0.14, 0.89)
Other	1.15 (0.95, 1.39)
Choice status – Yes	1.09 (0.98, 1.20)
Non VA prescriber	2.52 (2.25, 2.82)
Cancer diagnosis	1.37 (1.21, 1.54)
Opioid use disorder	1.86 (1.47, 2.35)
Drug use disorder (not opioids, tobacco)	1.00 (0.81, 1.24)
Alcohol use disorder	0.86 (0.72, 1.01)
PTSD	2.05 (1.83, 2.31)
Depression	1.63 (1.47, 1.82)
Bipolar	1.59 (1.35, 1.87)
Schizophrenia	1.47 (0.84, 2.58)

Limitations

- Use of Choice enrollees without confirmation that they used services under Choice
- Failure to exclude persons with terminal illness/ in palliative care, but did include cancer as a covariate

Conclusions from Our Data Analyses

- Non-VA prescribers independently increases the likelihood of risky opioid prescriptions in Kentucky Veterans prescribed opioids
- Recommendation: Standard of care of review of PDMP database prior to prescribing
- Ongoing challenge is sharing of diagnostic history
 - PDMP review will not help non-VA providers be privy to opioid use disorder diagnoses made in the VA

Summary

- Because of concerns over lack of efficacy and significant harms, VA has successfully reduced system-wide opioid therapy in conjunction with
 - Increased safety monitoring
 - Increased non-opioid pain treatments and
 - Increased access to treatment for opioid use disorder
- Yet, overdose rates continue to rise. This may in part be because of outside-VA opioid access.
- The sources of non-VA opioid access studied depends on the research question.
- PDMP data, combined with standard approaches to quantifying opioid exposure using prescription data, is a compelling approach for measuring outside-VA controlled substance receipt.

Thank you!

Questions?

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