UAB HEERSINK SCHOOL OF MEDICINE

The University of Alabama at Birmingham

Irrational Exuberance, Incautious Stoppage, Ethical Failure: Lessons from Our Prescription Opioid Story

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Physician, Birmingham Veterans Affairs Medical Center

Note

- This talk combines policy history, science and my views
  - Opinions are not positions of US Department of Veterans Affairs

- I don’t own pharma stock. I previously owned shares of CVS, sold in 2020, when I found my broker bought it that year
- My spouse owns shares of Johnson & Johnson, independently

- I turned down all requests to work in national opioid litigation

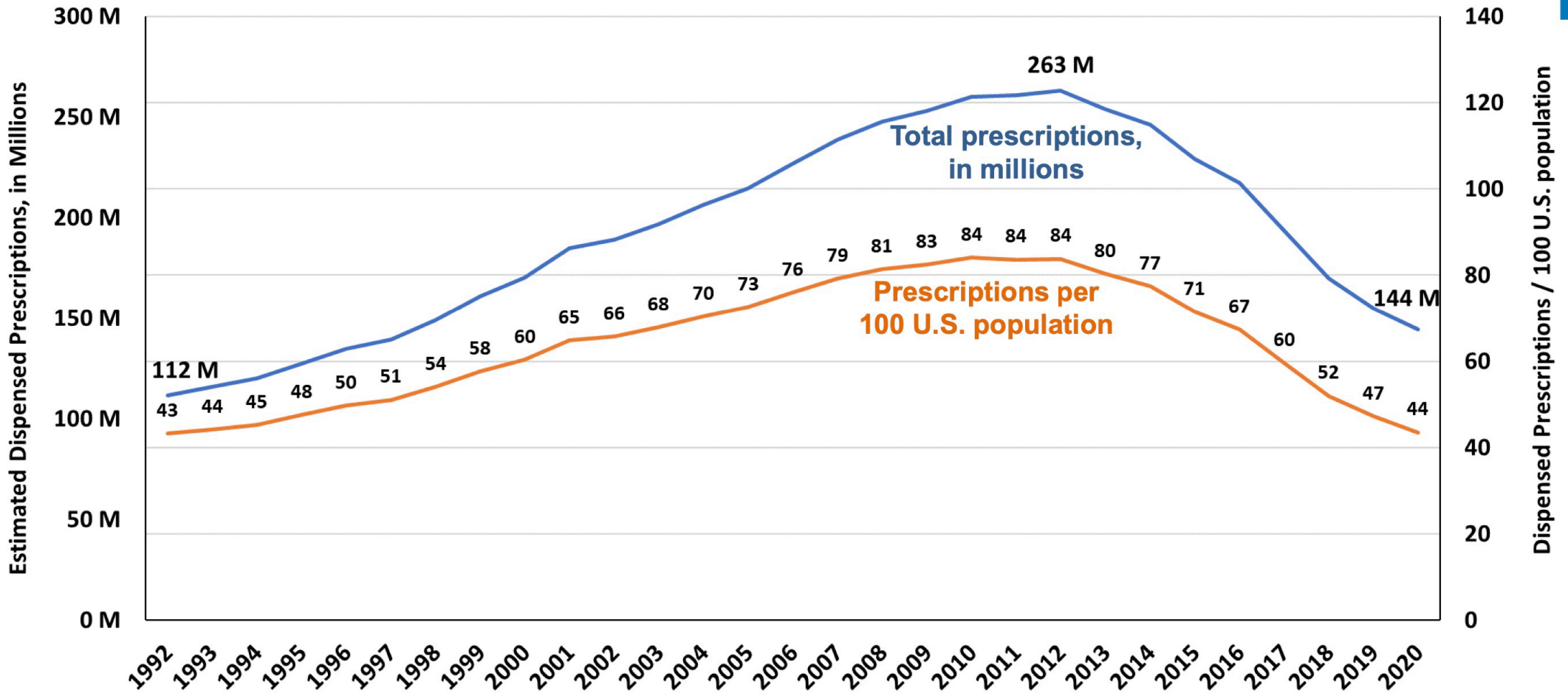
Based on the book by Beth Macy. Key points: ravenous marketing, denial by Purdue, not just poor/rural people, supply can induce demand, families who spoke up were opposed at every turn

Beth Macy, author of *Dopesick*

- **Many books** on the US opioid story
- Macy's "Dopesick" book includes well-off suburban + middle class
  - Defies expectations of who "falls through the cracks"
  - I felt outrage at Purdue, and kinship with the doctor
- Among most books on this crisis: patients with pain are **not** part of the story (this is a theme for today's talk)

Image from: C-ville.com 1/19/19

Large Declines in Opioid Analgesic Prescriptions



Estimated opioid analgesic prescriptions dispensed from U.S. outpatient pharmacies, total and per 100 U.S. population, 1992–2020.
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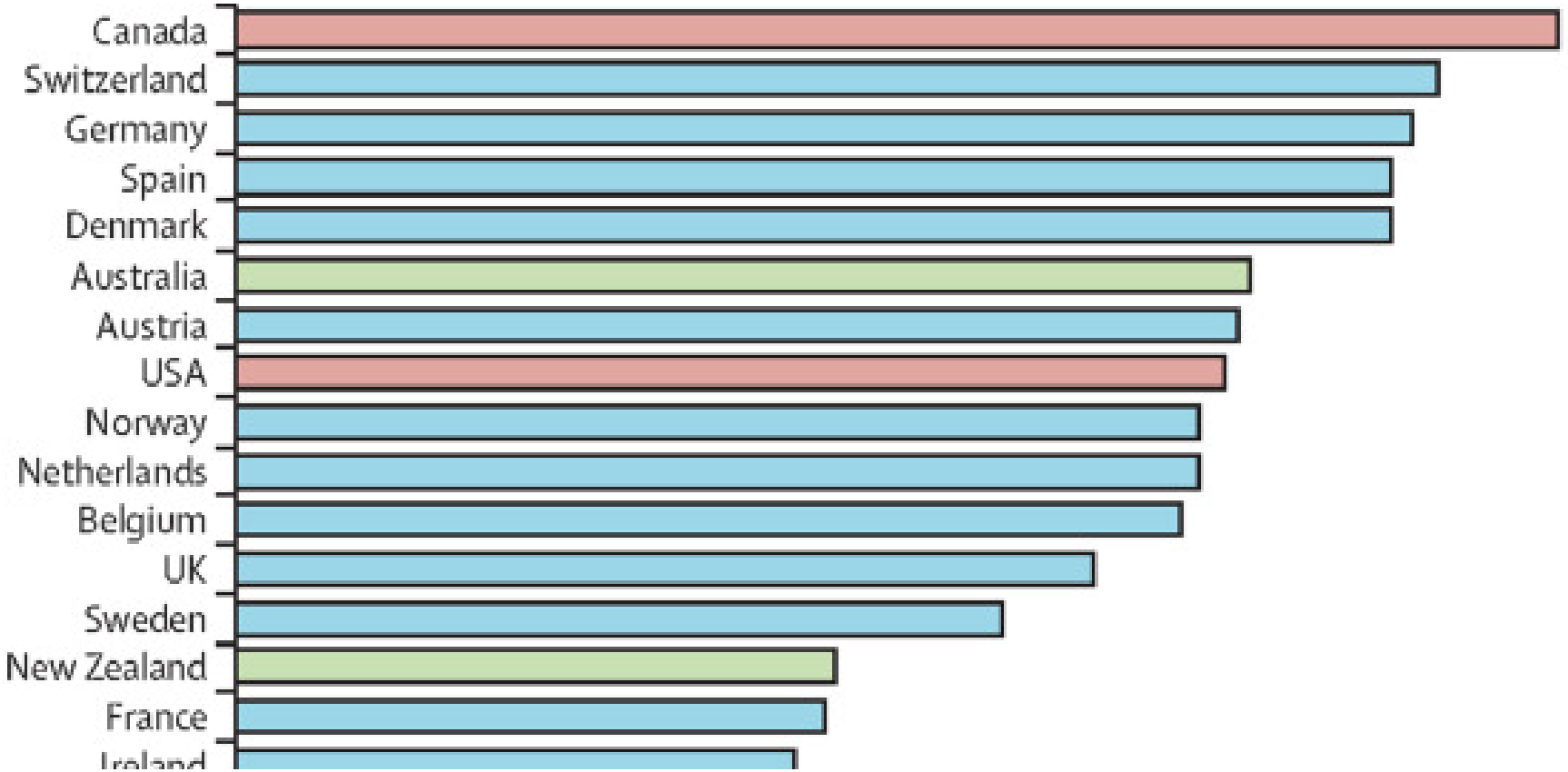
USA ranked 8th in per-capita opioid consumption, in 2019



Ju et al. *Lancet Public Health*. 2022;7:4:E335-E346 doi: https://doi.org/10.1016/S2468-2667(22)00013-5

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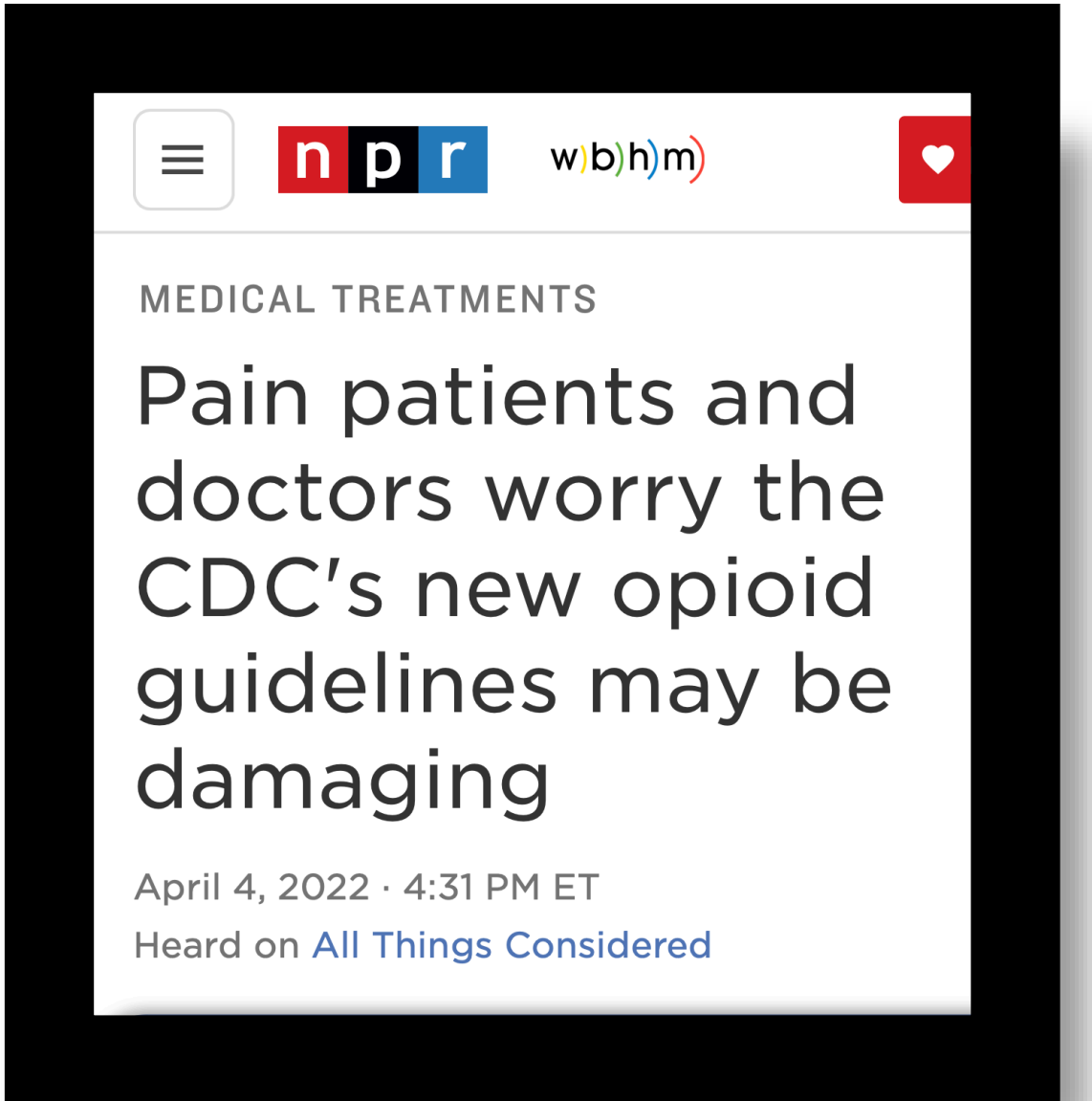
Emerging ramifications of our reduction



Agenda for This Talk

1: How did US policy embrace liberal prescribing of opioids?

2: How did US policy shift to a rapid reduction, focused on long-term recipients?

3: What's the evidence FOR or AGAINST taper or stoppage in long-term recipients?

4: A "clinical framework" for considering our care for patients with pain that puts safety guidance in that context

1: How did US policy come to embrace liberal prescribing of opioids?

A “Policy Monopoly” of the late 1990s

- “A **policy monopoly** is a collection of agents who control the definition of problems that deserve to be solved, voices that deserve to be heard and methods that deserve to be considered” h/t Cairney[1]
  - It included: doctors, FDA, other agencies, pharmacy leadership, medical educators, health care regulators, hospital and health system management
- People and agencies with aligned financial and ideological commitments usually work to counter opposing views

Kertesz & Gordon, *Addiction.* 2018. Summarizing Cairney P. Understanding Public Policy: Theories and Issues. Basingstoke, UK/New York: Palgrave Macmillan; 2012.

How did prescriptions rise?

- A push to address pain began in 1990s
- Pain as “5th Vital Sign” (e.g. US Dept of Veterans Affairs)
- Marketing & Weak regulation
  - Promotion of weak data about low addiction risk

- Pills always more profitable than other types of pain care
- The background was crucial: nonexistent training in pain, addiction, disability or rehabilitation among health professionals

Such advertising is **legal** in the US, a US policy that's problematic

Pain is presented as an orthopedic condition

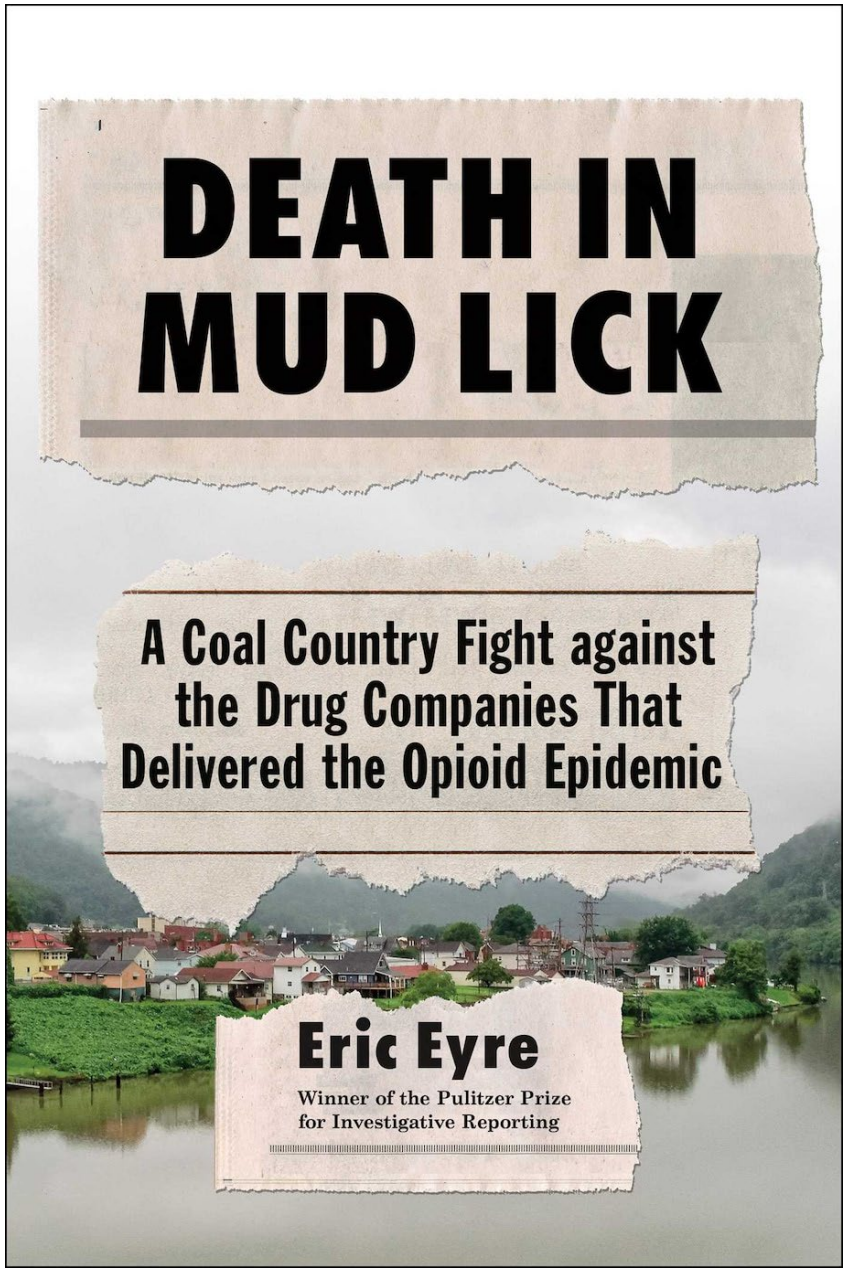
Implication: a pill makes stair-runners

The "**full 12 hours**" claim: internal Purdue data showed this often was not true

These pills, prior to reformulation, were easily broken to get an immediate (and enormous) dose in illicit users

Rivers of pills (WV)

- Kermit has 400 residents: in 10 months, 3m pills, 10,000 a day
- From 2006-2012, McKesson sent no suspicious order reports to DEA
- Ecosystem of pill mills, blithe pharmacies, lax DEA, redistribution
- Questions in Sally Satel's review:
  - how to reconcile structural causes of addiction (poverty, social malaise) with personal choice/agency of users & sellers?



Review from Washington Post by Sally Satel "Behind West Virginia's opioid crisis, an addiction to money" 4/23/20.
Eyre, E. Charleston Gazette-Mail. 12/19/18.

2: How did US policy shift to a rapid reduction of opioids, heavily involving long-term recipients with pain?

Governmental

- US Congress (SUPPORT Act, etc)
- US HHS FDA
- US Dept of Justice & DEA
- Provincial or State regulators
- Boards & Colleges

Framing Voices

- Key Journalists
- Advocates
- Government speakers
- Litigation
- Medical journals

Where are the patients?

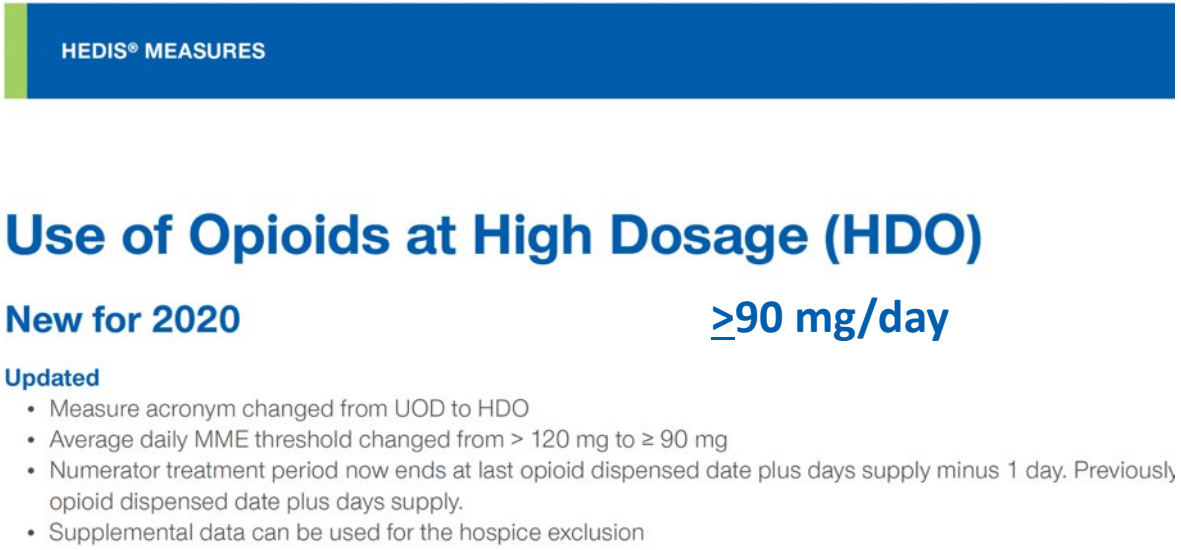
Guidances & Metrics

- CDC
- VA/DoD
- Canadian National & Provincial
- NCQA

Payors & Other Entities

- Pharmacy chains
- Pharmacy Benefit Managers
- Hospital Administration (and VA)
- Any hospital or chain
- Malpractice policy

Quality Metrics



- No exceptions for complex illness

- The metric **incentivizes** dose reduction across the board
  - ≥90 MME treated as bad care, in all instances
- Enforced by:
  - Payers (variously)
  - US Medicaid programs (variously)
- Built into:
  - Incentive payments (5-Star)
  - Legal investigation thresholds

Note: “HEDIS” is a product of National Committee for Quality Assurance (NCQA)

Uniform Agreement

Don’t stop
opioids rapidly

That was ignored in practice-
see next

Incautious stoppage 1

Abrupt Discontinuations[1]

- Long-term opioid recipients in Medicare Part D beneficiaries
- Discontinuation increased by 49% from 2012 to 2017 (5.7% to 8.5%)
- The proportion of stoppages that were abrupt rose from 70.1% to 81.2% from 2012 to 2017
  - Abrupt = final month >50% of prior daily dose

1. Neprash, JGIM, 2021: https://doi.org/10.1007/s11606-020-06402-z.
2. Long-term: ≥4 quarters with ≥60 days/qtr.
3. Discontinuation: 60 day cessation & no resumption for a year

Incautious stoppage 2

- In US national prescribing data
- Persons who started receipt of opioids in 2017-18 and attained high dose (>90 mg)
- Rapid = reached 0 mg after either
  - >40 mg on 1 day in 21 before stopping
  - >20 mg on 1 day in last 7 before stopping
- ***810,120 discontinuations, and 72% were rapid***

Stein, Brad (Rand). Rapid Discontinuation of Chronic, High-Dose Opioid Treatment for Pain: Prevalence and Associated Factors. J Gen Intern Med.

A Normal Question

- Is the problem that we're stopping a **problematic drug wrongly**?

Or

- Are are opioids **helpful** in ways we are afraid to say aloud?

Answer:

YES

Slight detour…

How bad or how good are opioids

- If we had some **other treatment** that routinely worked well for persons with severe long-term pain, opioids wouldn't be considered
- We don't, so we make **ethical tradeoffs** by choice
- Opioids' evidence in cancer or sickle cell is no stronger than in other conditions, and yet we grant an ethical leeway

- RCT summaries guide next 2 slides. My **warning**:
- RCT's valid- at a cost of not knowing the recovery context (patient, community)…[1]

1. Tucker & Roth. *Addiction.* 2006. https://doi.org/10.1111/j.1360-0443.2006.01396.x

Opioid Rx RCT summary (simplified)

- AHRQ: randomized trials with chronic pain (2020, update 2022)[1]
  - Opioids → small benefits vs placebo for pain or function 1-6 months
  - Lack of trials vs placebo >6 months
  - **On average** opioids do not outperform non-opioids (the relevant long-term comparative trial is by Krebs et al, 2018.

- German reviews: randomized trials (2019)
  - Osteoarthritis: no benefit vs placebo for relief>50% [2]
  - Low back pain: yes benefit vs placebo for relief >30%[3]
- *Some of AHRQ technical experts are paid witnesses in opioid litigation. One German author had speaking fees*

Chou et al. (for AHRQ, 2020) https://doi.org/10.23970/AHRQEPCCER229
Welsch et al (2019) Eur J Pain. https://doi.org/10.1002/ejp.1522
Petzke et al (2019) Eur J Pain. https://doi.org/10.1002/ejp.1519

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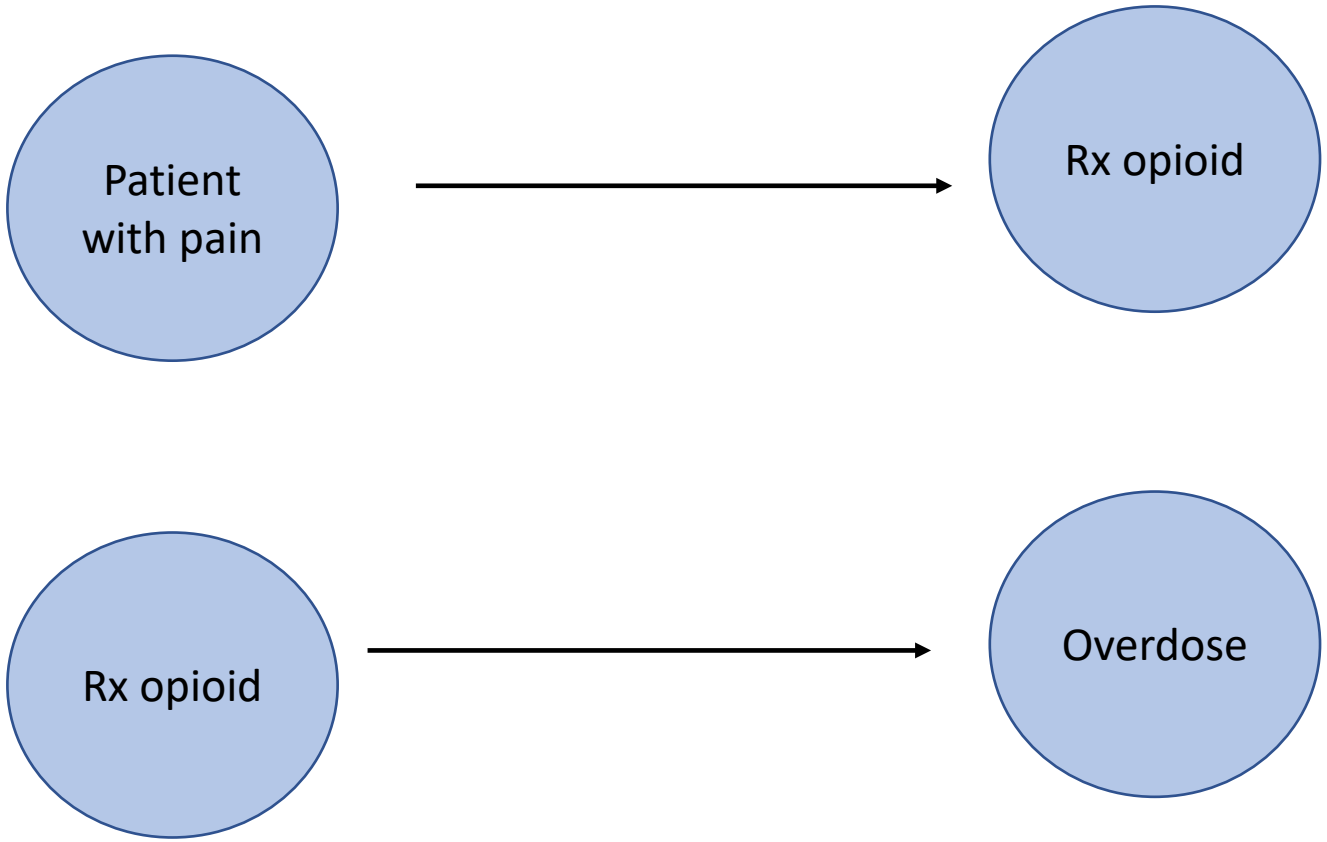
Outside of opioids, RCTs (2020 AHRQ)

- Non-medication treatments (233 RCTs, often N<70)[1]
  - Effect sizes “small”
  - Low back pain: psychologic therapies, small effect to 1 year
  - Knee: exercise no better than NSAIDs
  - Most <6 months

- Non-opioid medication (184 RCT’s, 13% “good quality”)[2]
  - Many medicines have short-term benefits
  - Long term: no treatment had large effect on pain or function

Skelly et al. (for AHRQ, 2020) https://doi.org/10.23970/AHRQEPCCER227
McDonagh et al (for AHRQ, 2020) https://doi.org/10.23970/AHRQEPCCER228

Simple lines I find unhelpful



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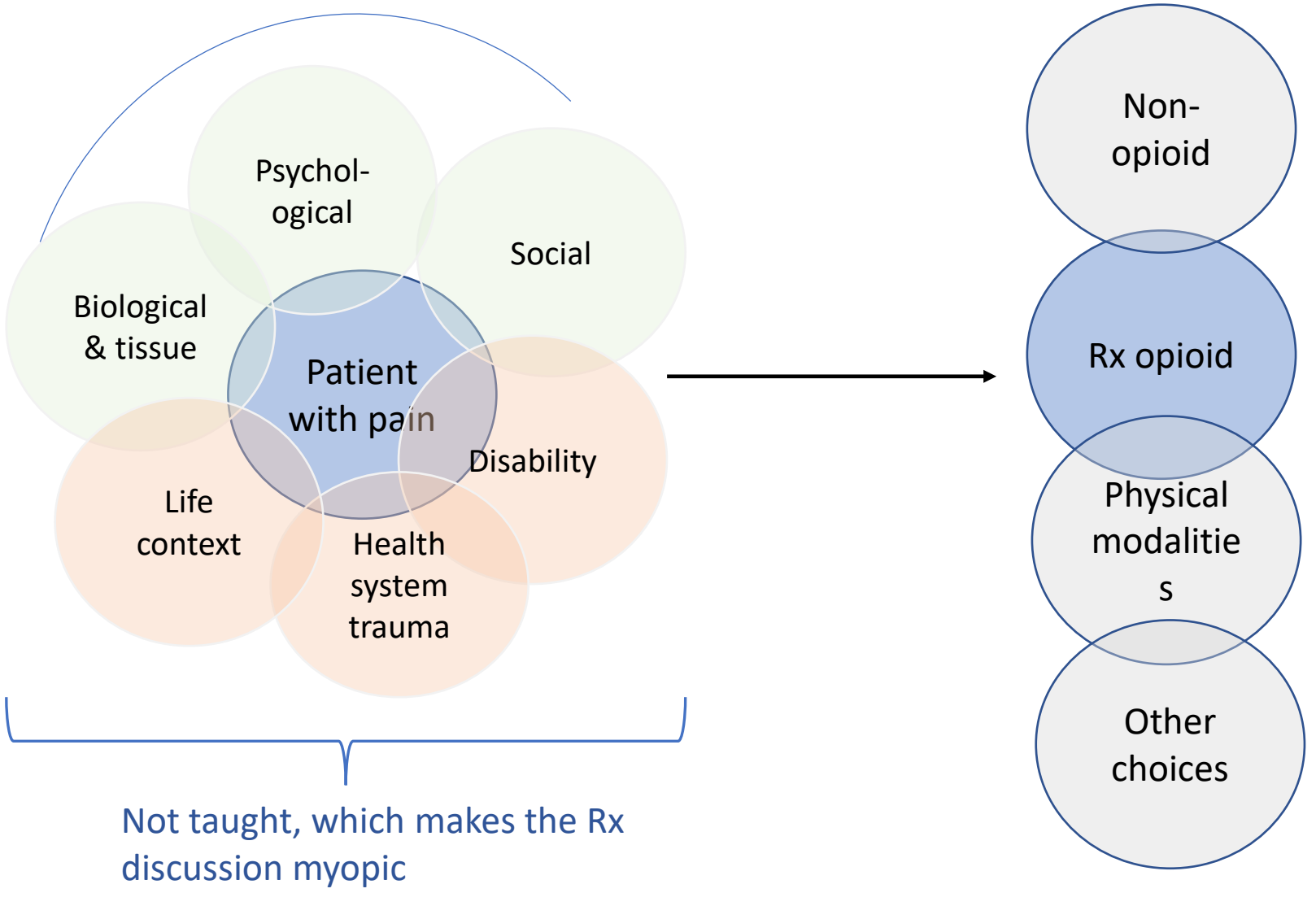
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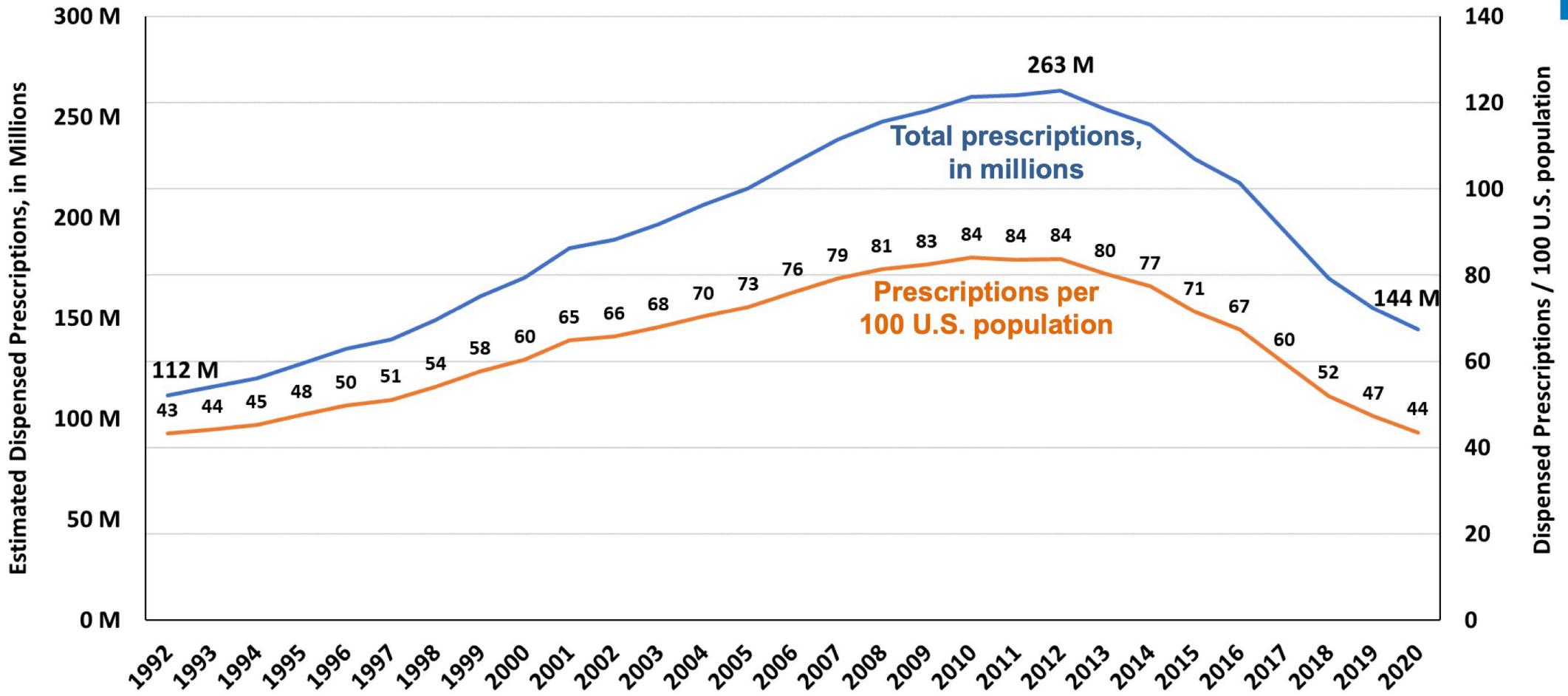

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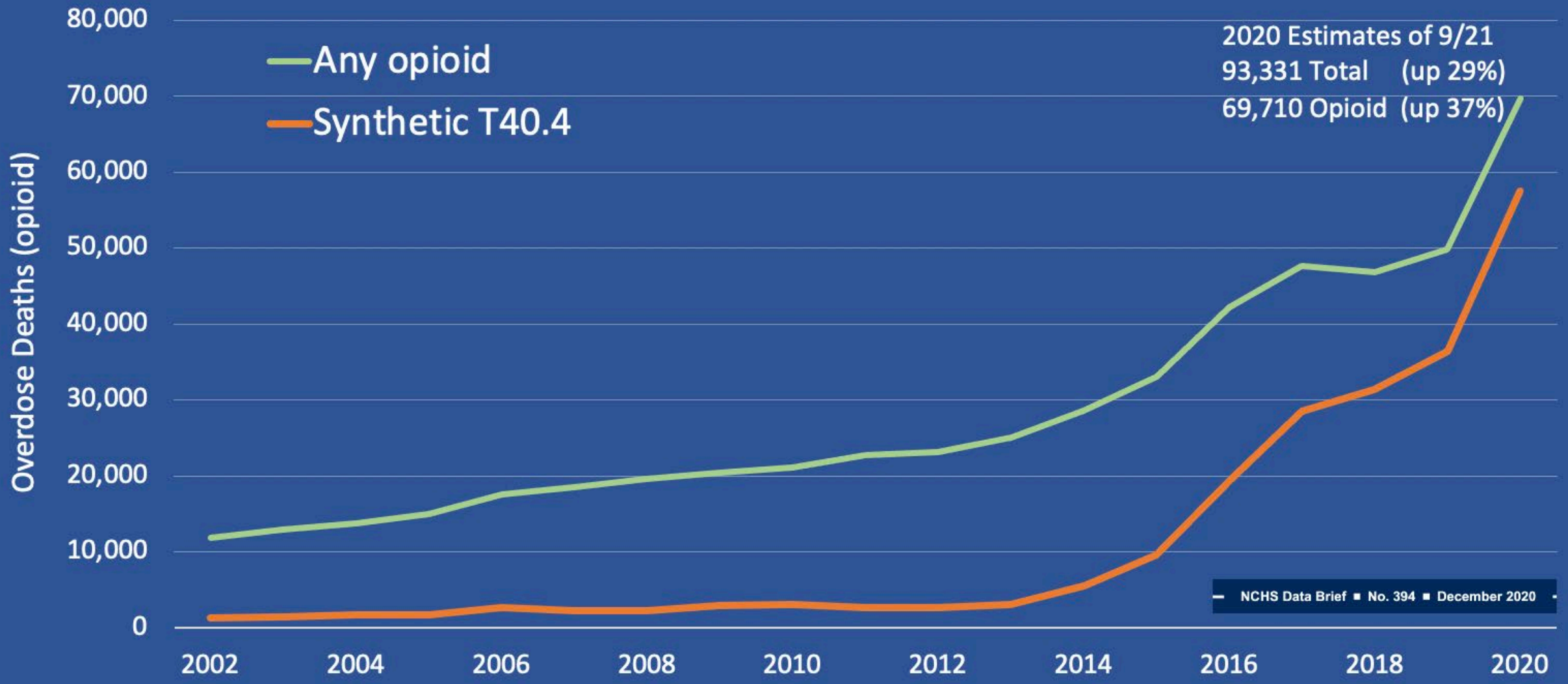
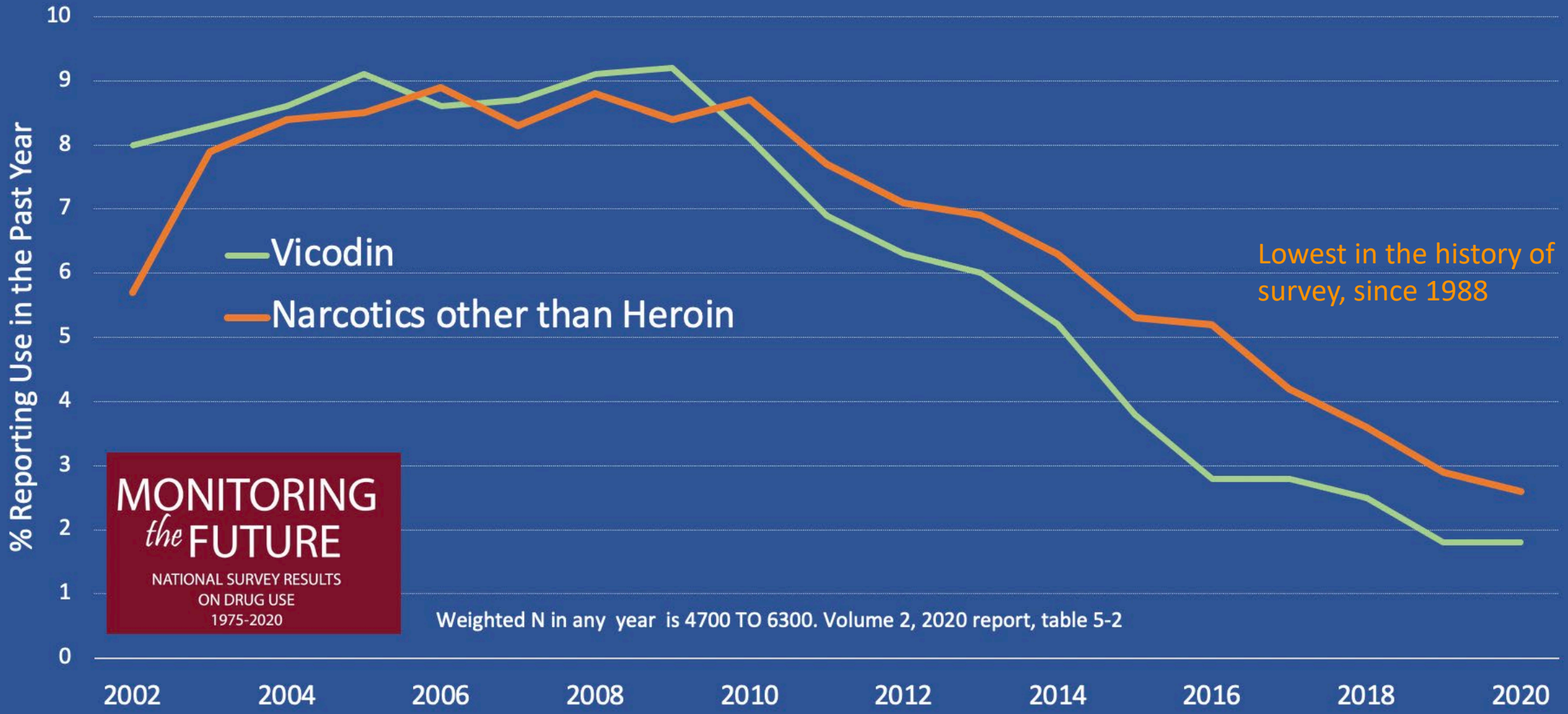
Opioid Overdose Deaths, USA (CDC/NVSS)



…what sustains today's crisis is not what launched it (Kertesz, *Turning the Tide or Riptide*, Subst Abuse J, 2017)

Past-year use of opioids (ages 19-30), Monitoring the Future



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3. What's the evidence FOR or AGAINST taper or stoppage in these long-term recipients?

What is an argument for taper or stoppage?

- There are risks to opioids
  - Risks correlate, retrospectively, with dose
  - VA outcomes from 2004-08
- Volatility of pain or emotion can develop on opioids
  - At one end of the spectrum: Opioid Use Disorder

Dose	**Overdose Deaths** Treating 1000 persons for a year
>100 MME	14.9
50-100	8.0
20-50	2.9
1-20	1.3

Bohnert, 2011. JAMA

Doesn't take into account co-prescribed sedating meds or any other facctor

Opioid taper or stoppage

- Frank (2017): 40 studies, including 5 RCTs with N=261 patients[1]
  - Most **short-term, voluntary, multimodal, high-touch service**
  - "very low-quality evidence that opioid dose reduction may improve pain, function, and quality of life"
- Mackey (2020): rapid review 49 studies with 19 more applicable to Veterans
  - net balance of benefits and harms of LTOT dose reduction "unclear"
  - also "unclear" for serious harms including substance use, opioid overdose, and suicide

(1) Frank. *Annals Int Med*. August 1, 2017. (2) Mackey. *JGIM*. Nov 2020

Observational work that could favor tapering

- VA EPOCH study[1,2]
  - 9253 Vets on long-term opioids, 2016-2017[1]
  - At baseline, >50% rated pain care **as fair or poor**, regardless of dose
  - No pain difference if dose dropped involuntarily vs voluntarily (n=290)[2]
- **VA comparison of discontinuers and continuers[3]**
  - For discontinuers, a decrease in a composite **adverse outcome**
  - Combined accidents/wounds, opioid + alcohol + non-opioid medication accients, overdosess and injuries (not death)
  - Changes to statistical modeling approach changed the results

1.Krebs et al. 2020. doi: 10.1371/journal.pone.0230751. 2. Frank et al 2021 doi: 10.1007/s11606-020-06294-z
3. Hayes C. Addiction. 2022. doi: 10.1111/add.15689
AOs: accidents with wounds/injuries, opioid-related and alcohol and non-opioid medication-related accidents and overdoses, self-inflicted injuries

What might disfavor tapering and stoppage?

- Opioids **not** "ineffective"[1]
  - AHRQ review (2022), finds **a benefit** (with limitations)

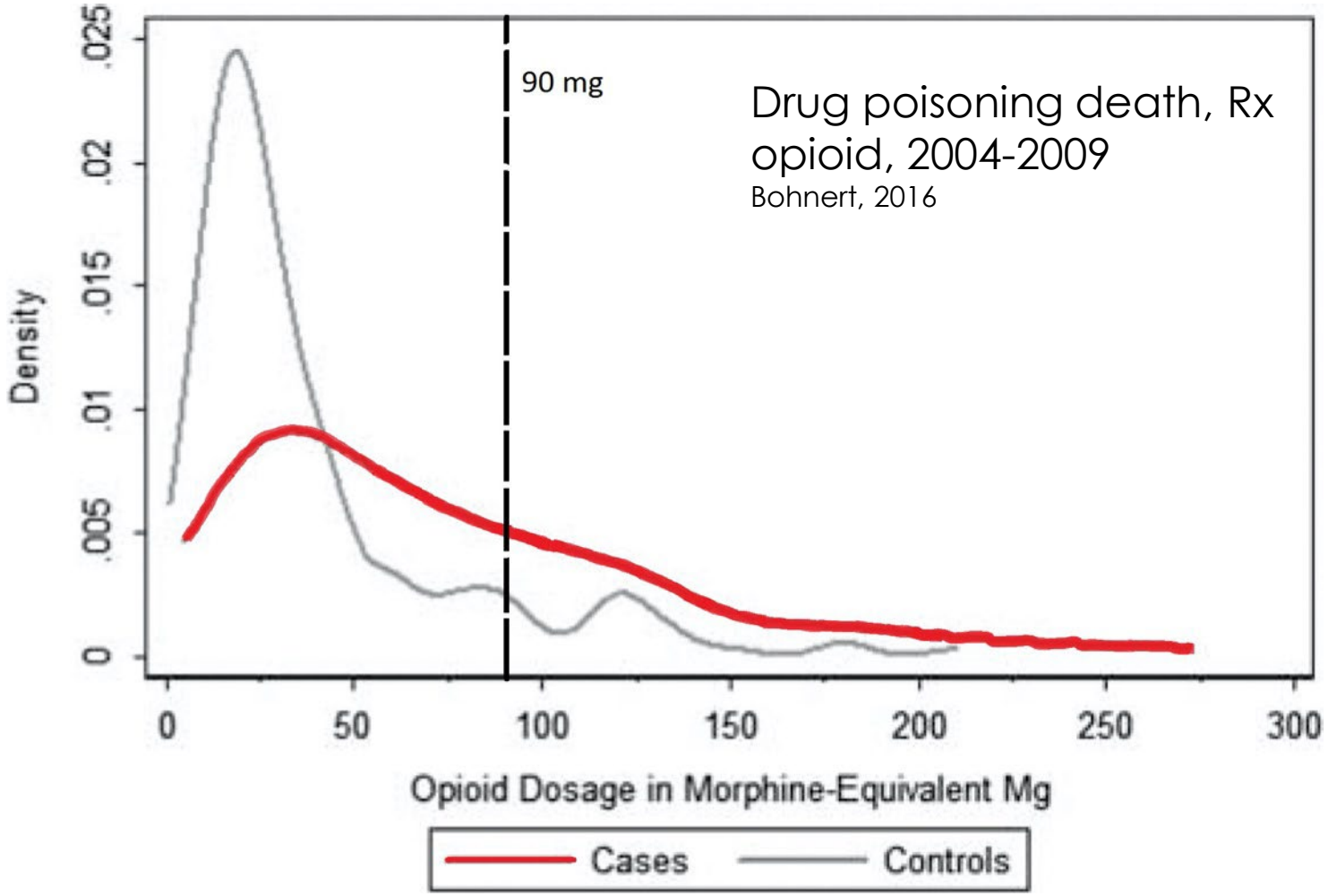
- Normally with complex decisions we try to individualize, discuss risks and seek informed consent

The science to come

- "Dose" is not the **primary** risk factor for the poisoning deaths
- Reduction or stoppage is associated with risk

1: AHRQ (Chou et al, 2020). https://doi.org/10.23970/AHRQEPCCER229; Petzke. *Eur J Pain.* 2019.https://doi.org/10.1002/ejp.1519 Bialas. *Eur J Pain.* https://doi.org/10.1002/ejp.1496

Most opioid drug poisoning deaths are at low dose



US Veterans:

a dose-based approach **misses most people at risk**…

And likely misses a good deal of **why they happen**

"Overdose" implies a simple pharmacy question

Bohnert, *Med Care*. 2016;54 (5): 435-41

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Opioid risk: Dose alone provides limited risk estimate

Daily morphine equivalents	Mental Health diagnoses	Medical Diagnoses Healthcare Utilization	CNS polypharmacy	Risk for overdose + Suicide/suicidal behaviors
Patient 1 20 MMED	Bipolar	Cardiac arrhythmia, HTN, DM-2, non-metastatic Cancer, Fe def. anemia	Tramadol	2.3%
Patient 2 60 MMED	Tobacco UD, Cannabis UD Bipolar, Anxiety disorder	HTN, Obesity Recent IP MH, ER visit	ER morphine	11.8%
Patient 3 90 MMED	AUD, Other SUD PTSD, Major depression, Agoraphobia with panic	Huntington's chorea	Fentanyl patch Diazepam Gabapentin	38%
Patient 4 240 MMED	OUD, Sedative UD, Tobacco UD, Mixed DUD, PTSD, Bipolar, ADHD	Cardiac arrhythmia, HTN, Sleep apnea Fall inuries, IP Detox, ER visit for suicide	ER morphine Zolpidem	58%
Patient 5 270 MMED	Tobacco UD Fear of injury	COPD ER Visit for suicide	ER morphine Duloxetine	4%

A simple plan of opioid and benzo taper unlikely to work

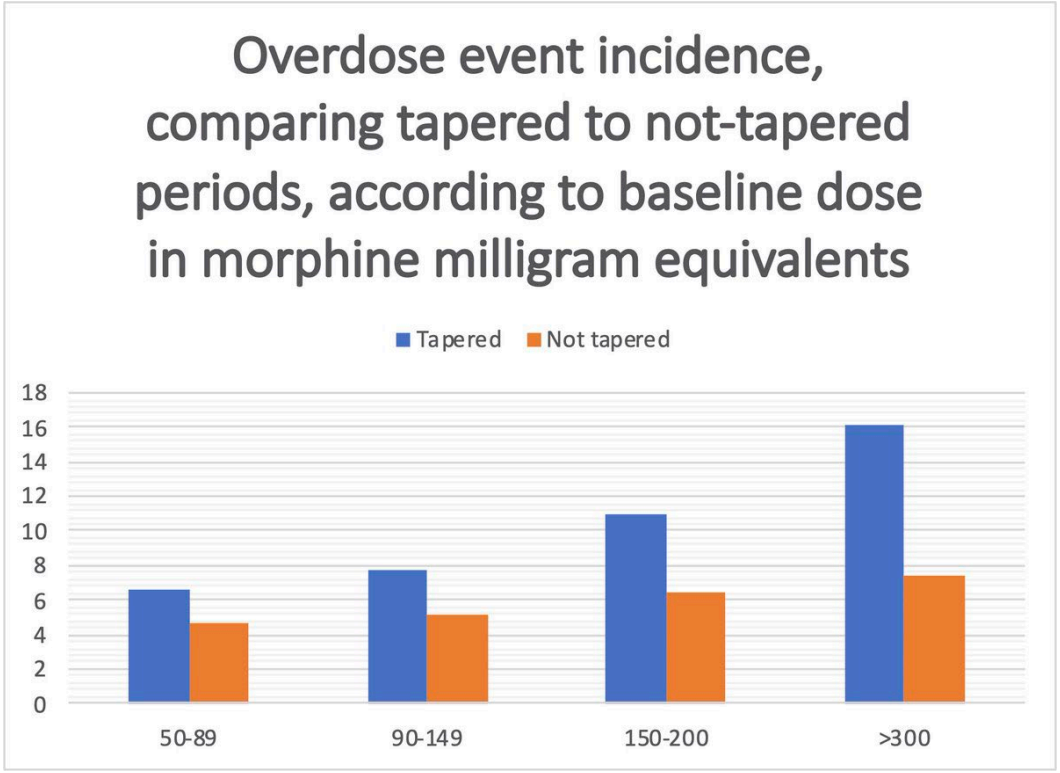
4 taper papers of concern

- Stoppage in Vets often followed by suicidal ideation/action (11.4%)[1]
  - *Not a comparative study*
- Dose variations associated with increased OD risk[2] *Kaiser Colorado (2006-2017)*
- Cessation from high dose in Vermont Medicaid (>120 MME) was usually in 1 day, with emergency care needed *(Mark, 2019)*
- Cessation associated with 3x risk of OD death, versus non-cessation *(James, 2019)*
  - *N=572 patients on long-term Rx opioids in Seattle clinic (2010-15)*

1.Demidenko. *Gen Hosp Psychiatry*. 2017:47: 29-35. 2.Glanz. JAMA Network Open. 2019;2(4):e192613
3. Mark. *JSAT*. 2019. 103:58-63 4. James JR. *J Gen Int Med.* 2019;34: 2749-55

3 *more* taper papers of concern

- Cessation in Oregon Medicaid associated with 3-5x elevated risk of suicide event[1]
- In VA data (2013-15) stoppage associated with increased overdose and suicide deaths[2]
- In US national data, taper associated with mental health crises and overdose events)[3]



1. Hallvik. PAIN. Online April 7, 2021.
2. Oliva E. BMJ
3. Agnoli. JAMA. 2021.

Research

Funding Notice of Award 10/19/21

VA | U.S. Department of Veterans Affairs

Veterans Health Administration

Health Services Research & Development Service

Clinical context of SuicIde following OPIOID transitionS:

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"We want to learn how to prevent these deaths from happening"

Allyson Varley, PhD

See our survey at go.uab.edu/csiopioids or call 1-866-283-7223 email: csiopioids@uabmc.edu

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2022

With retrospective comparisons

Many aspects of the clinical story are outside of the database

Evidence from retrospective analysis requires caution

It’s regrettable that this caution was absent when policies to incentivize, require, or induce dose reductions on otherwise stable patients were put in place

Part 4. My view of good care

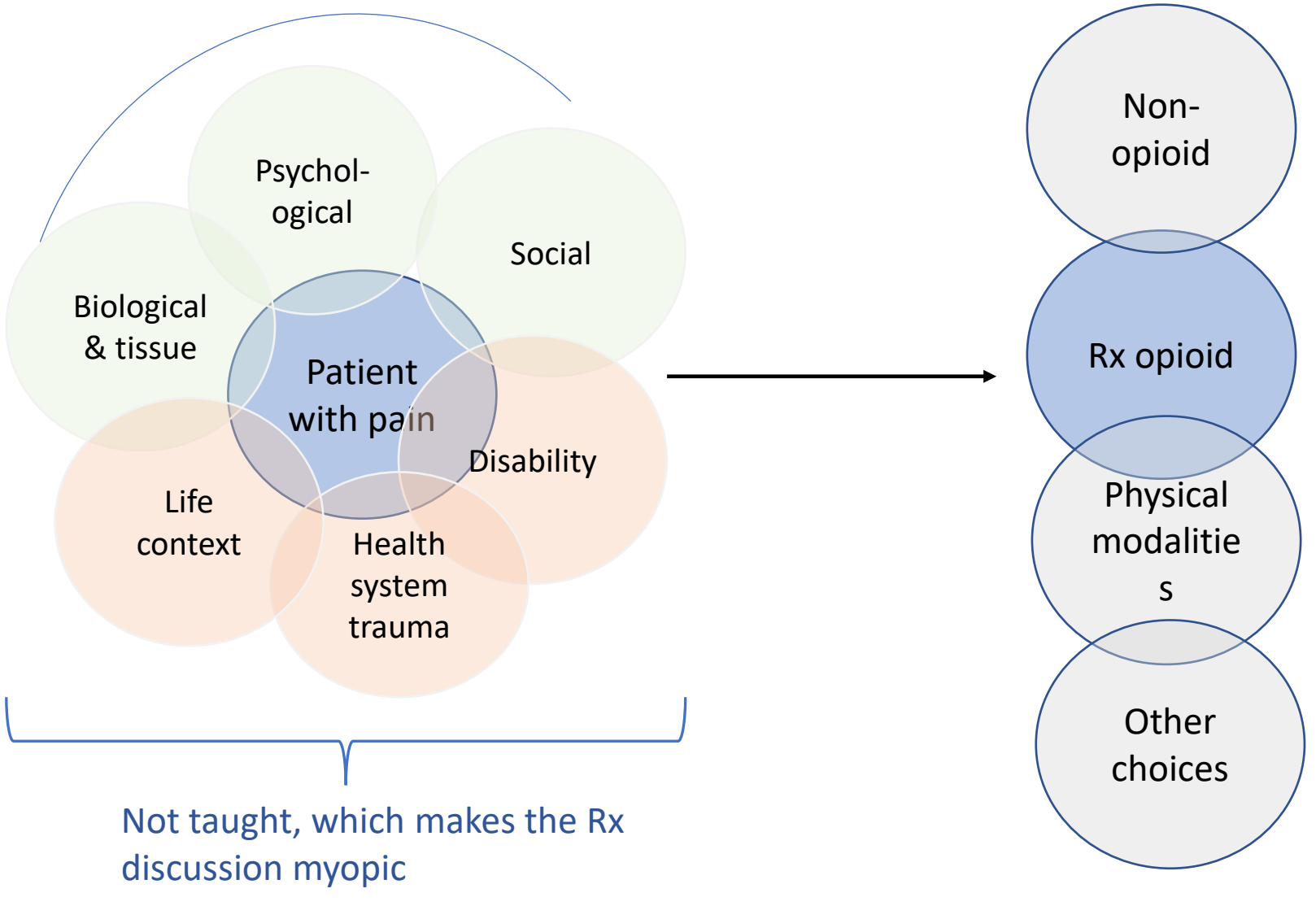
A caveat and a case

Caveat: discussions of pain care with opioids tends to become referendums on “the pills”

- Reasons for that “pill focus” are:
  1. Our poor underlying training on pain and disability
     - Can you imagine “scalpels, are we for or against?”
     - Or “antiarrhythmics: they cause arrhythmias, they don’t prevent them!
     - What do you automatically think?

  2. Honest discomfort with grey decisions
  3. Exploitation of 1 and 2 by pharma/Purdue
  4. Our reckoning with the failings of 3, 1, and 2

- We should use common Guideline safety tips and evidence but
- **Remember:** pain care is NOT the poison control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So is there something to use?

- **If the framework for care decisions is good,** most of the tips from CDC's 2016 Guideline are fine
- Rx dose-based risk idea is reasonable when assessing escalation (see earlier slides)
- Obvious strengths
  - Opioids are not firstline
  - It should be uncommon and **very** carefully justified if you combine with benzo
  - Carefully LEARN and then DISCUSS with patient the evaluation of risks and benefits, especially if opioids are being started or escalated
  - I favor **liberal** naloxone co-prescription (I'm required in my organization)
- Be thoughtful about the (usually required) urine tests & PDMP checks

One case

- Mr. Jones is a 56 year old man with osteoarthritis in multiple joints, and pain severity 7/10 most of the time and 9/10 at extremes
- Prior interventions included 2 surgeries that failed (knee and shoulder)
- His substance use issues: “heavy drinking” prior to age 35 or so, with a 5-drink binge about once a month “during SEC football, but sometimes NFL”
- Prior meds (NSAIDS, duloxetine, APAP) have failed
- There is some family anger that coincides with his telling you his pain is worse
- He is clearly trying to uphold a set of responsibilities.
- He did PT 2 years ago for 12 weeks. It helped a bit, briefly, but he tells you “it’s really far from where I work and not that useful anyway”

One case

Clinical Science: SPACE trial?

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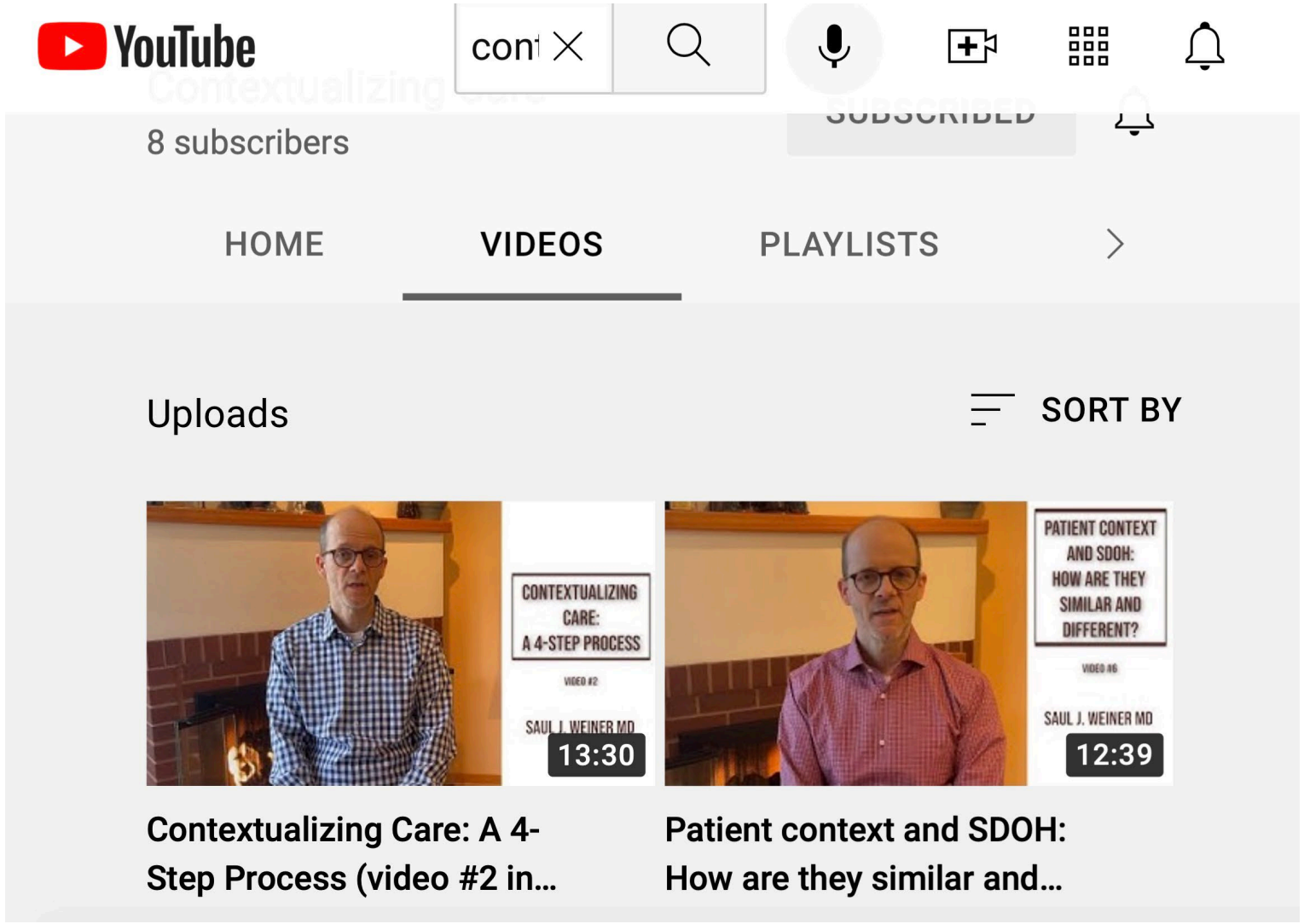
Pain Science?

- There is some family anger that coincides with his telling you his pain is worse
- He is clearly trying to uphold a set of responsibilities.
- He did PT 2 years ago for 12 weeks. It helped a bit, briefly, but he tells you “it’s really far from where I work and not that useful anyway”

Contextual

Contextualizing Care is a concept developed and tested by Dr. Saul Weiner (Veterans Affairs Health Services Research & Development)



Opioids and the physician-patient relationship: What are we getting wrong?

Podcast

New Episode

On Becoming a Healer is on all platforms (Spotify, Apple, etc) and at https://pod.link/healer

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Conclusions

- Our US opioid history reflects not just commercial forces but underlying deficits in health professional training
- US opioid prescribing fell rapidly in ways that reflect multiple influences at once, superimposed on our lack of training
- A lot of the reduction was not careful
- Evidence that tapering a long term recipient, against their will, makes them safer is at best: “unclear”
- Our care decisions should consider clinical history & patient context
- And they should involve a careful relationship

Irrational Exuberance Incautious Stoppage Discussion

Stefan Kertesz, MD
Steven Prakken, MD (No Disclosures)
Paul Martin, MD (No Disclosures)

Should These Be Considered "Safer" Opioids?

Opioid	MME/day	Cost for 30 8day Supply
Tramadol (Ultram) 50 mg QID CIV	20	$14
Tapentadol (Nucynta) 50mg QID CII	80	$960
Buprenorphine 2mg QID CIII (Off label for pain)	240*	$22
Fentanyl Patch (Duragesic) 25mcg/hr Q3d CII	60	$27
Codeine 30 mg QID CII	18 MME	$50

Atypical Opioids

- Opioids that are weak or partial agonist
  - Safer (SUD and pharmacologically)
  - First to be trialed if opioid indicated
  - Consider using in higher risk situations

- Tramadol (Ultram)
  - SNRI primary
  - Opioid minimal, in metabolite only
- Tapentadol (Nucynta)
  - NE and full agonist
  - 50-75mg = 10mg oxycodone *clinically*
  - 1/50th mu function of MS
- Buprenorphine
  - Partial agonist, ceiling effect
  - Transdermal Patch (Butrans)
  - Buccal (Belbuca)

AHRQ February 18, 2022

Nonopioid drugs (NSAIDs, Gabapentinoids, SNRIs)

associated with small to moderate improvements (0.5-2/10) in pain and function outcomes in patients with specific types of noncancer chronic pain in the short term, with few differences between drugs in a class or doses of a drug.

Evidence on intermediate- and long-term effects on pain, function, and quality of life is limited.

Nonopioid drugs were associated with increased risk of class-specific harms (e.g., gastrointestinal events with NSAIDS), with some patients withdrawing due to adverse events, suggesting that potential harms should be considered when selecting nonopioid drug treatments.

https://effectivehealthcare.ahrq.gov/products/nonopioid-chronic-pain/research

Antidepressants

- Bupropion (Wellbutrin)
- Levomilnacipran (Fetzima)
- Vilazodone (Viibryd)
- Duloxetine (Cymbalta)
- Fluoxetine (Prozac)
- Vortioxetine (Trintellix)
- Venlafaxine (Effexor)
- Sertraline (Zoloft)
- Citalopram (Celexa)
- Escitalopram (Lexapro)
- Paroxetine (Paxil)
- Mirtazapine (Remeron)

Most Stimulating

May Cause High SE

Use if Low SE

Most Sedating

May Cause Low SE

Use if High SE

Opioids

- Oxycodone
- Hydrocodone
- Fentanyl

- Buprenorphine
- Tapentadol (Nucynta)
- Tramadol (Ultram)
- Oxymorphone (Opana)

- Morphine
- Hydromorphone
- Methadone

Most Stimulating

May Cause High SE

Use if Low SE

Most Sedating

May Cause Low SE

Use if High SE

Atypical Med Reactions

- Atypical medication reactions
  - Expecting sedation, get stimulation
    - Opioids, topiramate, pregabalin, benzodiazepines, etc.
  - Expecting stimulation, get sedation
    - Stimulants, NE agents, bupropion, etc.
  - Generic medications

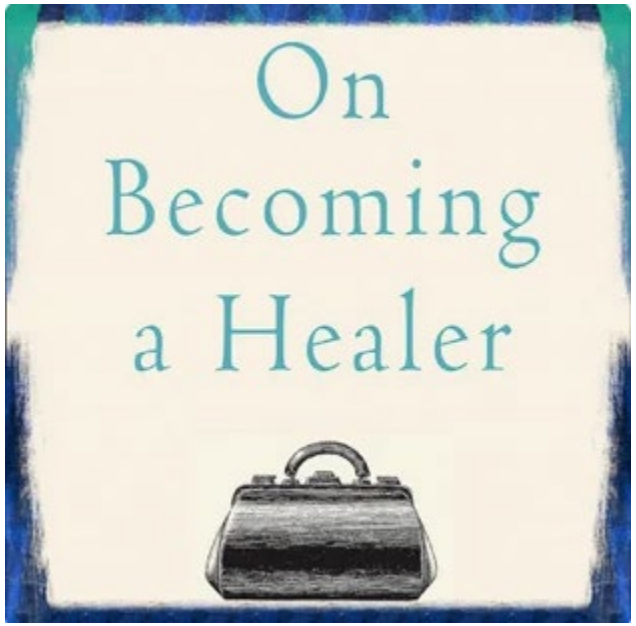
←May be part of functional benefit (a few examples)

- Unexpected tx with typical med reactions
  - Lyrica/Neurontin and anxiety tx
  - Benzo and spasm tx
- Unexpected tx with atypical med reactions
  - Opioid and ADHD tx or MDD augmentation
  - Buprenorphine and antidepressant effect
- If tapering these meds, then may need to replace unexpected tx to be successful in taper
  - Common with opioids

On Becoming a Healer – podcast

Stefan Kertesz, MD & Saul J. Weiner, MD

https://pod.link/healer/episode/f29f2af3510ca3a1b7663dd029775769



Questions?