A crisis of opioids, and the limits of prescription control: a conundrum

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Disclosures and a comment

- No pharmaceutical grants, honoraria, contracts, history of such
- I had stock in Abbot & Merck (<3%), sold it. My wife has same + J&J
- Opinions: not formal positions of any federal agency
- This talk may convey a “professorial certainty”. Nothing is fully settled
- I will mix cases where I was a caregiver versus not, but had full access to the record
Too many people are dying. The situation’s out of control. I kind of thought they were helping you, but right now I have to stop your Lortab pills. 

What did I do?
As proposed, for any person at total dose >90 MME

- Payment blocked at pharmacy
- Requires approval by Payer (e.g. United) or contracted agent (Magellan)

7-day limit for all "opioid-naïve" recipients
Letter of opposition, March 5, 2018

- First 180 signatures in 30 hours. ~220 by March 20, 2018
- 8 involved with CDC Guideline (2016)
- “Too cruel” – President of Physicians for Responsible Opioid Prescribing (Ballantyne)
“The decision to taper opioids should be based on whether the benefits for pain and function outweigh the harm for that patient,” said Dr. Joanna L. Starrels, an opioid researcher and associate professor at Albert Einstein College of Medicine. “That takes a lot of clinical judgment. It’s individualized and nuanced. We can’t codify it with an arbitrary threshold.”
A thesis of sorts

- I hope we can agree:
  - opioids were vastly overprescribed through 2010-12
  - doing so caused harm
  - a systems-level decline in opioid reliance is desirable, broadly speaking

- My thesis:
  - Forced opioid reductions are now quasi-mandated
  - They violate ethical and evidentiary norms of medicine
  - All agencies party to this trend must act to protect a population we are harming in the name of solving a social crisis
Overview

- Case Example
- Epidemiology of overdose and prescribing
- Pill control policies
- Data for and against
- My concerns
73 yo man with kidney transplant

- Chronic pain/polyarthritis from late 1990’s, renal transplant 2003
- Opioids since 2001, doses \~105-140 MME
  - Pre 2014: methadone + oxycodone
  - 2014: MD switched methadone to Morphine SA based on “VA appears to be getting away from methadone”
  - 2015: Morphine SA ended, left with oxycodone 30 mg daily
  - 2016: “hurts all the time”
    - oxycodone 30 (45 MME) dropped to hydrocodone 7.5 tid (22.5 MME)
- 3/2017: admitted to hospital progressive renal failure
73 year old man continued

- Progressive loss of energy over months → inability to keep up with his meds to protect the transplant

- Past history:
  - 1970s: 2 psych hospitalizations for depression
  - Alcohol use disorder, did not drink since 1989 (one brief lapse)
  - Married twice, divorced. 5 kids out of state

- Evaluation
  - Renal biopsy: acute and chronic rejection
  - Acute rejection is prevented by the meds this patient lost the ability to manage
73 year old man

- March 2017
  - Temporary dialysis—restabilized
  - Bumped opioids to oxycodone 10 mg four times a day (60 MME)
    - Told local PCP not to change
- May: reduced to hydrocodone 7.5 three times a day
- Readmitted twice in next 6 months
- Died September 2017
- Hydromorphone (Dilaudid) 0.4 mg/hour for the last 24 hours

- Was this patient protected by the taper he received?
Interpretation

Clinical

- This is **not** acute withdrawal
  - Slow taper prevents that
- This is protracted abstinence syndrome
  - Resurgent pain
  - Psychological dependence
  - These are intertwined
  - Slow taper may work for some and be totally useless for others

Policy Context:

- This is not really VA-specific
- This man’s care is a response to public data
Epidemiology
Alcohol for 2014
121,000 deaths
(indirect + direct)
All CDC

Total U.S. Drug Deaths
Opioids about 2/3

More than 64,000 Americans died from drug overdoses in 2016 -- 64,070

CDC: https://www.cdc.gov/nchs/products/databriefs/db294.htm
Drugs Involved in U.S. Overdose Deaths, 2000 to 2016

by Stefan Kertesz, MD (UAB) skertesz@uabmc.edu

Fentanyl + heroin

Prescription-type
Our opioid prescriptions.

CDC, 2011: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm

by Stefan Kertesz, MD (UAB)  skertesz@uabmc.edu
My estimates combine two public reports from slightly different commercial databases: QuintilesIMS (per CDC, 2017) and IQVIA (2018).
US Opioid Overdose Deaths and Total US Opioid Prescriptions (2010-2016)

Opioid Overdose Deaths Tabulated by CDC: https://www.cdc.gov/nchs/data/databriefs/db294_table.pdf#page=4
Total Opioid Prescriptions from Pezalla et al, 2017: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5319424/
Graph prepared by Stefan Kertesz, MD  https://tinyurl.com/y8tvx2
Pain care?
Opioids?
Opioids for pain are:

- Crummy Drugs
- Not Spawn of the Devil
- Sometimes Quite Helpful
- Sometimes Last, Best Option

by Stefan Kertesz, MD (UAB) skertesz@uabmc.edu
An untidy record

- Why crummy?
  - 30%-60% stop due to side effects
  - 0.6-7% new onset addiction (1)
  - 3% - 20% seem to have problematic behaviors (2, 3)
  - Not routinely superior to stepwise non-opioid care for patients with musculoskeletal pain entering a randomized trial (4)

- Why not spawn of the devil?
  - Effective in trials of limited duration (5)
  - About 25%-33% stay on them long term at stable dose (6)

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

- Try to avoid starting
- Evaluate/document risks and benefits when starting
- Go for lowest effective dose
  - Cautious review when escalating ≥50 and ≥90 MME

- For patients already on opioids, evaluate harm vs benefit
  - No dose target, no mandated taper

- Monitor urine drug test, Prescription Drug Monitoring program

- Evidence quality: Low
Pill Control Policy

Hint: It's not really what the CDC guideline says in its text
Two Epidemiologic Hopes

**Overdose**
- Overdoses protection by reducing Rx doses (shielding)

**Addiction**
- Addiction will be prevented by prescribing less (preventing)
Pill Control Ascendant

- Quality Metrics on dose
- Payer restrictions
- Prescription Drug Monitoring
  - No warrant for search
- Pharmacy Red Flags
- Law enforcement
- Medical Board Rules
- Employer Rules
- FDA plans “new hoops” for doctors (12/2017)
To track against the 25 percent metric, Cigna measured the total volume of opioids being prescribed based on morphine milligram equivalent doses, taking into account the number of pills, the dosing of those pills, as well as the relative strengths of the different opioid medications.
Our decision to deny coverage for this medication(s) is therefore unchanged. Our decision does not reflect any view about the appropriateness of this medication(s). Only you and your provider can make decisions about your care.

Claire A. Horn, M.D., UnitedHealthcare Medical Director, specializing in Internal Medicine and Rheumatology reviewed your appeal. This decision was made based on UnitedHealthcare Pharmacy Clinical Pharmacy Programs-Prior Authorization/Medical Necessity - Long-Acting Opioid Pain Medications-Includes both brand and generic versions of the listed products unless otherwise noted: Arymo ER\(^\text{a}\) (morphine sulfate extended-release), Avinza\(^\text{a}\) (morphine sulfate extended-release capsules), Embeda\(^\text{a}\) (morphine sulfate and naltrexone), Exalgo\(^\text{a}\) (hydromorphone extended-release), fentanyl transdermal\(+\), Hysingla ER\(^\text{a}\) (hydrocodone extended-release), Kadian\(^\text{a}\) (morphine sulfate sustained-release capsules\(^\text{a}\)), Morphabond ER\(^\text{a}\) (morphine sulfate extended-release), morphine sulfate (generic MS Contin\(+\), MS Contin, Nucynta ER (tapentadol extended-release), Opana ER (oxymorphone extended-release), OxyContin\(^\text{a}\) (oxycodone controlled-release\(^\text{a}\)), Troxyca ER\(^\text{a}\) (oxycodone and naltrexone extended-release), Vantraela ER\(^\text{a}\) (hydrocodone bitartrate extended-release), Xtampza ER (oxycodone extended-release), Zohydro ER (hydrocodone extended-release)\(^\text{+}\).

You asked for coverage for Xampza Extended Release (ER) 36 milligrams (mg) at a dose of one capsule taken twice daily. This dose equals 72 mg per day. You are using this drug for chronic pain. This medicine belongs to a class of drugs called opioids. The amount of opioid that you take in a day is called the morphine equivalent dosage (MED). We reviewed your health plan language, benefits, and plan guidelines. We reviewed information sent on appeal. Your health plan covers up to 90 MED per type of opioid medicine per day. For Xampza ER that would be up to 54 mg per day. Your health plan only covers a higher dose if you have cancer-related pain or an end-of-life diagnosis. So, the prior denial is upheld.
If you have reduced or stopped prescribing opioids, what was the main reason for doing so?

- Most docs reducing opioid Rx’s do so based on rules, fear, hassles of care (59%)
What data support dose restriction on patients with chronic pain?
Bohnert, 2011

- Prescription Opioid OD deaths, unintentional, 2004-2008
- Restricted to deaths where Rx contributed, in whole or in part
- Dose was a risk factor

Findings
- Voluntary + well-run programs
- Dose reduction can be achieved for some patients
- Some do feel better
- "low quality evidence"

Limitations
- No studies of mandatory, involuntary opioid discontinuation
- Insufficient evidence on adverse events such as "overdose, switch to illicit opioids, onset of suicidality"

Frank et al. Annals of Internal Medicine. August 1, 2017
Sum up

- Voluntary taper with strong support seems to allow dose to go down
- Average pain doesn’t rise in such settings
  - But it does for some
- No data to suggest safety is increased
What data might not favor our focus on tapering high dose?

WHO OVERDOSES?
WHAT DO WE KNOW ABOUT TAPER?
VA FY2013 Overdose/Suicide Mortality

VA-wide analysis presented at 2018 National Rx Drug Abuse and Heroin Summit

MH/SUD-related factors account for 36% of the index. Model ORs:
- SUD = 12.7
- Bipolar/SZ = 2.8
- Benzo = 2.3
- Antidep = 2.2

Opioid-related factors account for 36% of the index. Model ORs:
- Fentanyl = 3.7
- Methadone = 2.8
- ER/LA = 1.7
- ≥100 MED = 2.0

Table 3: CIP-based risk index for serious opioid-induced respiratory depression (RIOSORD)

<table>
<thead>
<tr>
<th>Question</th>
<th>Points for &quot;yes&quot; response</th>
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| In the past 6 months, has the patient had a health care visit (outpatient, inpatient, or ED) involving any of the following health conditions?  
  - Substance use disorder (abuse or dependence)?  
  (This includes alcohol, amphetamines, antidepressants, cannabis, cocaine, hallucinogens, opioids, and sedatives/anxiolytics)  
  - Bipolar disorder or schizophrenia?  
  - Stroke or other cerebrovascular disease?  
  - Kidney disease with clinically significant renal impairment?  
  - Heart failure?  
  - Nonmalignant pancreatic disease (e.g., acute or chronic pancreatitis)?  
  - Chronic pulmonary disease (e.g., emphysema, chronic bronchitis, asthma, pneumoconiosis, asbestosis)?  
  - Recurrent headache (e.g., migraine)?  
| 25                                                                        |
| Does the patient consume:  
  - Fentanyl?  
  - Morphine?  
  - Methadone?  
  - Hydromorphone?  
  - An extended-release or long-acting formulation of any prescription opioid?  
  - A prescription benzodiazepine?  
  - A prescription antidepressant?  
| 13                                                        |
| Is the patient's current maximum prescribed opioid dose ≥100 mg morphine equivalents per day?  
  (Include all prescription opioids consumed on a regular basis)  
Total point score (maximum = 146)                                             |
| 75
MH/SUD and Non-Opioid Related Factors Have Higher Odds Ratios than Opioid-Related Factors in VHA Predictive Model

Odds Ratios for Overdose/Suicide-Related Events

Risk increased slightly with increasing MEDD
- e.g., 120 MEDD would increase modeled risk by about as much as a PTSD or AUD diagnosis

STORM Analysis: Oliva et. al. Psych. Services 2017
Dose did not predict OD in this Rx population (2018)

- ~43,000 Kaiser patients on Rx opioids
- The following predicted OD death
  - History substance use disorder
  - History mental illness
  - Tobacco
  - Long-acting opioids
- NOT dose

Glanz, 2018. JGIM. ~43,000 Kaiser patients who qualified as chronic opioid recipients, 2006-2014
Who Receives High Doses? People with risk factors needing care

- Multiple pain diagnoses
- Psychiatric diagnoses
  - E.g. depression, PTSD
- Substance Use Disorder, present or remitted
- Higher rates of Polypharmacy:
  - Antidepressant
  - Benzo
- Caveat: some people at high dose have none of these factors

Does taper work? Not with Prescription opioid use disorder

- Prescription opioid use disorder (n=653)
- RCT, funded by NIDA
- Tapered, with or without buprenorphine
- Voluntary
- Most started with pain (no heroin)
- One year failure rate for taper: 91.4%
Since 2010: hi-dose Opioid Rx Down 46%

OD with natural/semisynthetic opioids (excluding heroin/fentanyl):
Down 0.04%

Overall Natural & Semisynthetic figures from CDC: https://www.cdc.gov/nchs/data/databriefs/db294_table.pdf#page=4
Excluding Heroin & Synthetics from National Center for Health Statistics NVSS, by Clayton Hale, American Enterprise Institute
Clinical ethics of forced taper

- Do we ordinarily take
  - nonconsensual action on patients,
  - who are adherent and stable,
  - absent strong evidence for those actions
  - that sometimes result in the patients’ death?

- Do we let others induce physicians to take such action?

- Is we answer “no, not usually” then we must ask if we have a justification so powerful as to overcome customary medical ethics
Why we should be concerned
The personal side of pain: Meredith Lawrence

Chronic pain sufferer commits suicide after being cut off

By: Briona Haney
Posted: Nov 06, 2017 05:09 PM PST
Updated: Nov 06, 2017 05:09 PM PST
The crackdown on opioid use is having a real impact on veterans. A new study published in the Journal of the American Medical Association (JAMA) found that hundreds of thousands of veterans were forced to taper their opioid use, leading to severe withdrawal symptoms. This is particularly challenging for veterans who served in conflicts where they were exposed to traumatic events, as they rely on opioids to manage their pain.

According to the study, the VA has been systematically reducing opioid prescriptions, leading to a nationwide shortage of medication. This has resulted in veteran patients experiencing severe withdrawal symptoms, including nausea, vomiting, diarrhea, sweating, agitation, and tremors. The study found that veterans who were forced to taper their opioids were more likely to experience these symptoms compared to those who were able to maintain their medication levels.

The VA has faced criticism for its handling of the opioid crisis, with some veterans and advocates calling for more accessible treatment options. The new study highlights the need for a more comprehensive approach to managing opioid use, particularly for veterans who have complex medical needs.

In response to the findings, the VA has announced plans to increase access to tapering programs and to work with other healthcare providers to better support veterans in managing their pain. The study authors call for more research into effective tapering strategies and the development of more patient-centered care plans.
Dear Dr. Kertesz,

I've kept a standard list of suicides known to happen after nonconsensual taper or discontinuation. My own private list includes names and contact information for at 58 deaths where suicide happened after cessation or taper of opioids in a pain patient who had received them long term. I also am aware of at least 103 cases where I am uncertain as to contact information or formal name, but I would consider collaboration with public health authorities if there is interest in understanding what has happened to these individuals. Some may have been reported by more than one individual so determining an exact number is difficult, but I'm confident of at minimum 103 cases.

Sincerely,
The Pain Refugees

The forgotten victims of America’s opioid crisis

By Brian Goldstone
Responses to these concerns

- CMS
  - Changed plan for 2019
  - Has received 4 briefings and has requested a CMS Grand Rounds
- Insurers
  - Hints of concern
- Some prominent advocates
  - Have asked if I am funded by pharma
  - Pointed out that opioids are associated with suicide
  - Have suggested we have insufficient data to justify investigating the deaths
My suggestions to the CDC, 6/2017

are these controversial?

- Clarify CDC’s 7th recommendation re: persons already on opioids
- Assemble stakeholders to gauge implementation, as urged by CDC’s Opioid Guideline Workgroup of January, 2016
- Investigate the outbreak of suicides and public suicidal ideation

Philadelphia: June 9, 2017
CHERISH Conference
Leonard Davis Institute & University of Pennsylvania
Investigation of a Youth Suicide Cluster in Kent and Sussex Counties – Delaware, 2012

Final Report

8 suicides among youth
CDC investigated

Prepared By:

Katherine A. Fowler, PhD, EIS Officer
Alexander E. Crosby, MD, MPH, Medical epidemiologist
Sharyn E. Parks, PhD, Epidemiologist
Asha Z. Ivey, PhD, EIS Officer

by Stefan Kertesz, MD (UAB) skertesz@uabmc.edu
May 1, 2018

58 with names and contact information
103 inclusive where contacts uncertain

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Sincerely,
Let’s ask this:

- If harm is happening, why would a public agency not be willing to investigate, despite being asked directly?

- Is there something about the lives of people who have received long-term opioids for pain that makes their lives or deaths not worth measuring and investigating?
Regulators, Payers should correct course

- **Safe Harbor**: pull back from policies that force dose reductions*

- Dose reductions don’t address most OD risk, anyway
- We can and should invest in enhanced care for multi-morbid populations
  - Mental + Medical + Addiction
  - Social Vulnerabilities

- **In Primary Care**

*As disseminated by many, including NCQA, NQF, Pharmacy Quality Alliance, most major private insurers, state regulations (e.g. Maine), and major health employers"
Opioid Pill Control vs Pill Pushing

- Today’s pill control and yesterday’s pill pushing
  - are mirror images of each other
  - they embody a thirst for simple solutions
  - they enable a failure to build systems of care for populations at risk

- Zeitgeist phrase “opioid stewardship”
  - What about the **people**?
EXTRA SLIDES