Opioid Prescription Control: When the Corrective Goes Too Far

Satellite Conference and Live Webcast
Wednesday, March 21, 2018
12:00-1:00 p.m. Central Time

Produced by the Alabama Department of Public Health
Video Communications and Distance Learning Division

Faculty

Stefan G. Kertesz, MD, MSc
Diplomate, American Board of Addiction Medicine
Associate Professor, University of Alabama at Birmingham
Member, Opioid Safety Initiative at Birmingham VAMC
@StefanKertesz

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" that reflects my best reading of data. Nothing is fully settled**

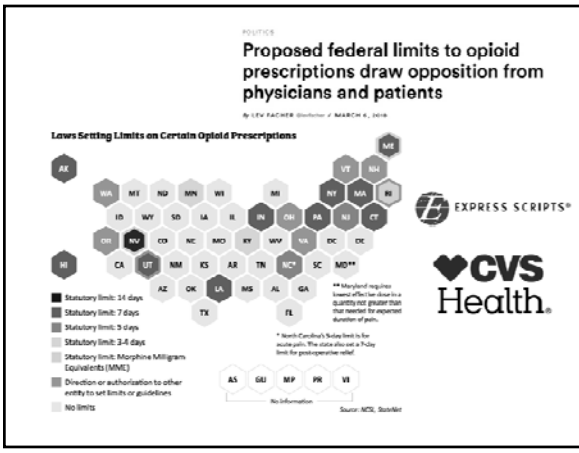
Disclosures and a Comment

- **This talk includes learning from several, which does not mean they agree with every thought offered here**

Adam J. Gordon, MD
VA Salt Lake City
U. Utah

Ajay Manhapra, MD
VA Hampton HCS
Yale U.

Sally Satel, MD
American Enterprise Institute
Yale U.



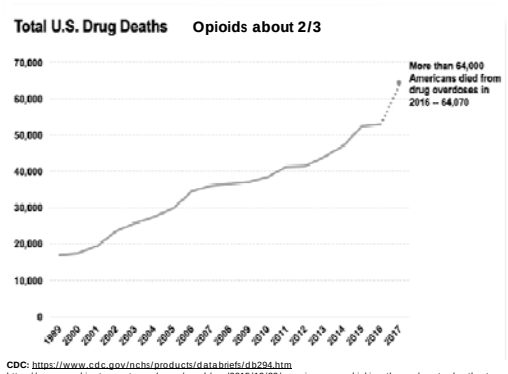
Our decision to deny coverage for this medication(s) is therefore unchanged. Our decision does not reflect any view about the appropriateness of this medication(s). Only you and your provider can make decisions about your care.

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^ (morphine sulfate extended-release), Avinza^ (morphine sulfate extended-release capsules), Embeda^ (morphine sulfate and naltrexone), Exalgo^ (hydromorphone extended-release), fentanyl transdermal+, Hysingla ER^ (hydrocodone extended-release), Kadian^ (morphine sulfate sustained-release capsules^), Morphabond ER^ (morphine sulfate extended-release), morphine sulfate (generic MS Contin)+, MS Contin, Nucynta ER (tapentadol extended-release), Opana ER (oxymorphone extended-release), OxyContin^ (oxycodone controlled-release^), Troxyca ER^ (oxycodone and naltrexone extended-release), Vantrela ER^ (hydrocodone bitartrate extended-release), Xtampza ER (oxycodone extended-release), Zohydro ER (hydrocodone extended-release) +May not apply to all states. The determination is as follows:

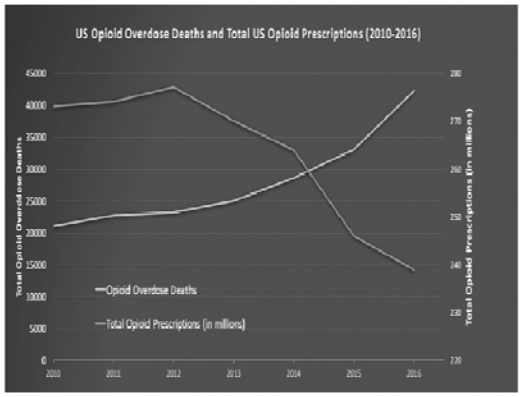
You asked for coverage for Xtampza Extended Release (ER) 36 milligrams (mg) at a dose of one capsule taken twice daily. This dose equals 72 mg per day. You are using this drug for chronic pain. This medicine belongs to a class of drugs called opioids. The amount of opioid that you take in a day is called 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 Xtampza 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.

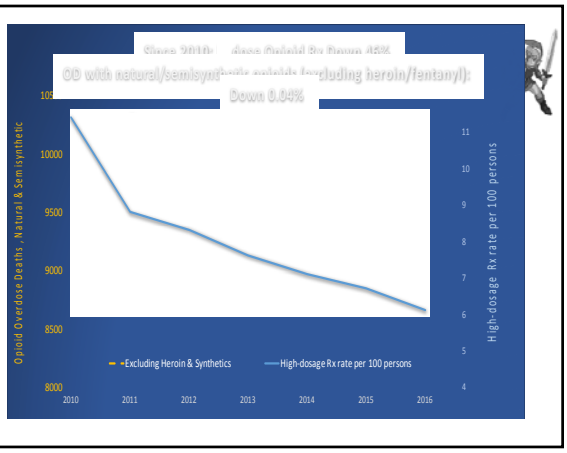
Structure

- Evolution of US Opioid Crisis
- Introduce reasonable pain care
  - CDC Guideline & opioids
- Describe opioid pill control initiatives
- Describe the problems with overcorrection



CDC: https://www.cdc.gov/nchs/products/databriefs/db294.htm
https://www.washingtonpost.com/news/wonk/wp/2015/12/22/americans-are-drinking-themselves-to-death-at-record-rates/?utm_term=.b4451a80435f





A crisis changed

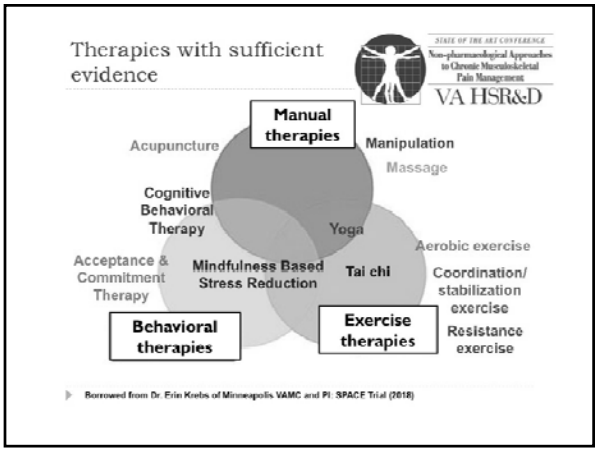
- About ¾ of the opioid-related overdose deaths in 2016 involved heroin or fentanyl
- About ¼ involved a possibly prescribed opioid, without any heroin or fentanyl
  - Not necessarily prescribed to person who died

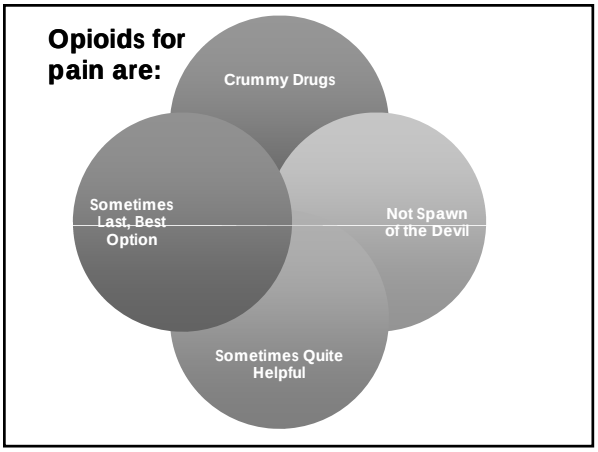
Pain care? Opioids?

What about chronic pain then?

- 23.4 million: severe and debilitating chronic pain (1)
- 5-8 million: on chronic opioids (2)
- Chronic pain can be terrible experience for some & associated with suicide (3)
- Any and all proposed treatments for chronic pain
  - Predominantly short-term data
  - Works for a minority
  - With modest benefit

1. Nahin RL. J Pain. 2015 (NHIS data). 2. NIH, 2014. 3. Ilgen, JAMA Psy. 2013.





An untidy record on opioids

- Why crummy?
  - 20%-60% of patients stop due to side effects
  - 0.6-7% new onset addiction (1)
  - 3% - 20% seem to have problematic behaviors (2)
- Why not spawn of the devil?
  - About 25%-33% of patients stay on them long term after randomized trials, usually at stable dose (3)

Aren't they no better than Tylenol according to a recent study?

- For adults with hip, knee or low back pain (n=248)
- Who volunteered to be in a trial
- These two treatment arms did about as well as each other

JAMA | Original Investigation

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

Erin E. Krebs, MD, MPH; Amy Gravely, MA; Sean Nugent, BA; Agnes C. Jensen, MPH; Beth DeRonne, PharmD; Elizabeth S. Goldsmith, MD, MS; Kurt Kroenke, MD; Matthew J. Bair; Siamak Noorbaloochi, PhD

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

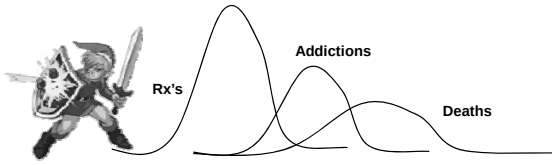
- Try to avoid starting if possible
- Evaluate/document risks and benefits when starting
- Go for lowest effective dose
  - Cautious review when escalating ≥50 and ≥90 MME
- Follow-up regularly
- For patients already on opioids, evaluate harm vs benefit
  - No dose target
- Monitor urine drug test, Prescription Drug Monitoring program
- Evidence quality: Low

The rise of pill control

Two Epidemiologic Hopes

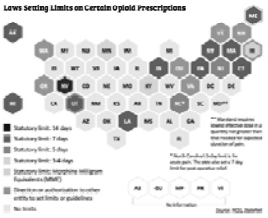
Overdose
- Overdoses protection by reducing Rx doses (shielding)

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)



CVS Health

CMS Proposal for 2019

- Deny payment at point of sale if cumulative MED >90
  - Allow prior authorization
  - Exceptions: hospice, metastatic cancer

"We are proposing important new actions to reduce seniors' risk of being addicted to or overdoing it on opioids while still having access to important treatment options," said Demetrios Kouzoukas, CMS deputy administrator and director of the Center for Medicare, on a phone call with reporters. "We believe these actions will reduce the oversupply of opioids in our communities."

Med Page Today, February 1, 2018

What data support dose restriction initiatives?

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

Table 3. Cox Proportional Hazards Models of Risk of Death by Prescription Opioid Overdose[a]

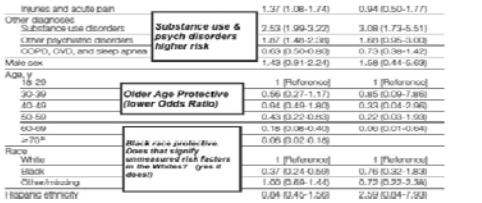
Predictors of OD in Veterans Rx'd opioids long or short term Bohnert, JAMA. 2011:1315-1321

	Risk of Opioid Overc	
	Chronic Pain (n = 111 758)	Cancer (n = 36 803)
Opioid fill type		
Regularly scheduled only	1 [Reference]	1 [Reference]
As needed only	1.10 (0.85-1.43)	2.75 (1.31-5.78)
Simultaneous as needed and regularly scheduled	1.34 (0.99-1.79)	1.84 (0.83-4.05)
Maximum prescribed daily opioid dose, mg/d		
1-<20	1 [Reference]	1 [Reference]
20-<50	1.99 (1.30-2.97)	1.74 (0.69-4.35)
50-<100	4.63 (3.16-6.74)	6.01 (2.99-15.78)
≥100	7.16 (4.85-10.65)	11.99 (4.42-32.54)
Pain-related diagnoses		
Cancer	0.99 (0.72-1.36)	
Chronic bodily pains	0.69 (0.35-1.33)	1.53 (0.74-3.16)

Dose is a risk factor in this study

Bohnert JAMA 2011. Apr 6;305(13):1315-21. doi: 10.1001/jama.2011.370.

- Substance use disorder, psychiatric disorder predicted risk
- No one knows what was given at time of death
- Being younger: high risk
- Among Veterans, white race was higher risk
  - suggests other unmeasured risk factors that differed by race



Bohnert JAMA 2011. Apr 6;305(13):1315-21. doi: 10.1001/jama.2011.370.

Annals of Internal Medicine

Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy: A Systematic Review

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

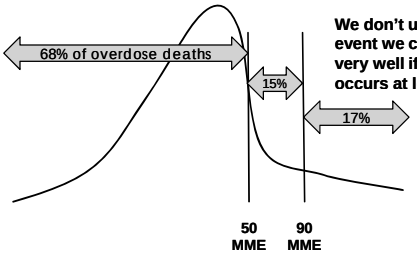
Guidelines differ on taper

- CDC Rec #7 (2016)
  - "If benefits do not outweigh harms of continued opioid therapy,
    - VA/DoD Algorithm D (2017):
      - Taper, absent consent, if:
        - Dose>90 MME
        - Co-prescribed benzodiazepine
        - Patient non-participation in "comprehensive pain care"
        - Other

What data might not favor mandating dose reduction

…AND WHAT'S THE THEORY BEHIND THE DATA?

Distribution of Overdose Deaths (n=842) According to Prescribed Dose, Among Veterans Prescribed Opioids in Fiscal Year 2013 (n=1,395,056)



We don't understand the event we call overdose very well if it mostly occurs at low dose

77% of Veterans dying had a substance use disorder or mental health diagnosis. Data from by PERC, simplified graphic from data approved for submission.

But relatively, risk is *higher* at high dose, right?

- Not always
- Probably? In many large databases
  - Co-prescribed and non-prescribed sedating agents emerge
- Rx dose:
  - A risk factor in VA data, but
  - Not clearly the dominant risk factor
  - Not a risk factor in Kaiser data
- Take a look at who receives high doses on average

What is the event called overdose, that we are trying to prevent?

ABSTRACT

From "Heroin Overdose" by Shane Darke in ADDICTION. 2016: 2060-63

Background and aims This narrative review aims to provide a brief history of the development of the heroin overdose field by discussing a selection of major 'classics' from the latter part of the 20th century. Methods Papers considered landmarks were selected from 1972, 1977, 1983, 1984 and 1999. Results Findings of earlier works suggest much of what later research was to demonstrate. These include arguing that overdoses occurred primarily among tolerant older users, that most 'overdose' deaths involved low morphine concentrations, that most overdoses involve polypharmacy, that drug purity has only a moderate influence on overdose rates and that instant death following heroin administration is rare.

Prescription risk factors

- Opioid type: Long-acting higher risk
- Risk increased slightly with increasing dose in MEDD
  - For example, 120 mg MEDD (vs none), would increase modeled risk by about as much as a PTSD or alcohol use disorder, at any dose
- Co-prescription of sedatives increased risk by 1.4 times
- Rx other classes of evidence-based but sedating pain medications (i.e., SNRI, TCA, anticonvulsants)
  - 1 additional class = 2.1 times the risk
  - 2 additional classes = 3.6 times the risk
  - 3 additional classes – 6.1 times the risk

Strong diagnostic and health care event risk factors for overdose or suicide-related events

Risk factor	Odds Ratio	Model Parameter
Prior overdose or suicide-related event	25.1	3.63
Detoxification treatment	18.3	2.96
Inpatient mental health treatment	16.6	2.81
Sedative use disorder diagnosis	11.1	2.33
Stimulant use disorder diagnosis	8.1	2.17
Opioid use disorder diagnosis	8.0	2.1
Non-drug substance use disorder	8.0	2.13
Cannabis use disorder	5.9	1.7
Bipolar disorder	5.8	1.82
Alcohol use disorder	5.3	1.56
Other mental health disorder	5.3	1.73
Major Depression	4.8	1.62
Emergency Department visit	3.4	1.22
Either accident	2.5	1.11
PTSD	2.6	1.24
Tobacco use disorder	2.2	1.08
AIDS	2.2	1.01
Liver Disease	2.2	1.05
Other neurological disorder	2.1	1.08
Electrolyte disorders	2.0	1.0

From Oliva, Elizabeth

Prediction Model for Two-Year Risk of Opioid Overdose Among Patients Prescribed Chronic Opioid Therapy

- Among 43,000 Kaiser patients who received prescription opioids
- The following predicted overdose death
  - History of substance use disorder
  - History of 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 in Large Database analyses?

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

Morasco, Pain. 2015. Kobus, J Pain. 2012.

Dose did not predict OD in this Rx population (2018)

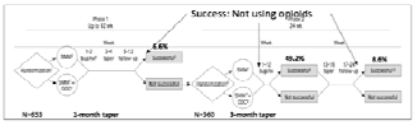
- ~43,000 Kaiser patients on Rx opioids
- The following predicted OD death
  - History substance use disorder
  - History mental illness
  - Tobacco
  - Long-acting opioids
  - NOT dose

Prediction Model for Two-Year Risk of Opioid Overdose Among Patients Prescribed Chronic Opioid Therapy

Glanz, 2018. JGIM. ~43,000 Kaiser patients who qualified as chronic opioid recipients, 2006-2014

Does taper work? Not with the addiction end of that spectrum

- 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%



Meredith & Jay Lawrence Story

Public story
Written consent provided
Detailed review of medical record + interview

8 LasVegasNOW.com
SECTIONS NEWS WEATHER

The personal side of pain: Meredith Lawrence

Chronic pain sufferer commits suicide after being cut off

By: Briana Haney
Posted: Nov 06, 2017 05:08 PM PST
Updated: Nov 06, 2017 05:09 PM PST

Meredith & Jay Lawrence Story

Background

Car crash + hard physical labor 1990s
Alcoholism
2005: stopped drinking, met future wife Meredith
2007: loss of feeling in his legs, blackouts, falls
2007-2010: mult back surgeries + opioids + bdz + implanted stimulator + intrathecal pump
2012: dx: trauma induced dementia
2013: correction for pump broken lead
2013-15: panic attacks

All info: consent, personal record review, expert record review, interview with Ms. Lawrence

Meredith & Jay Lawrence Story

Regimen 2016

Morphine 120 mg po daily
Intrathecal morphine 19 mg/day + clonidine
From PCP: alprazolam 2 mg po bid (down from 6 mg bid)

Meredith's story

Pain was always present
Disability high
Good days: walk the dogs, outings to WalMart, prepared coffee for his wife
Bad days: pain with tears running down his face

The taper 2/3/2017

Morphine po 120->90
"State & federal guidelines"
Insisted on termination of all alprazolam
Plan for 60 mg on 3/2/2017, 45 mg 1 month later

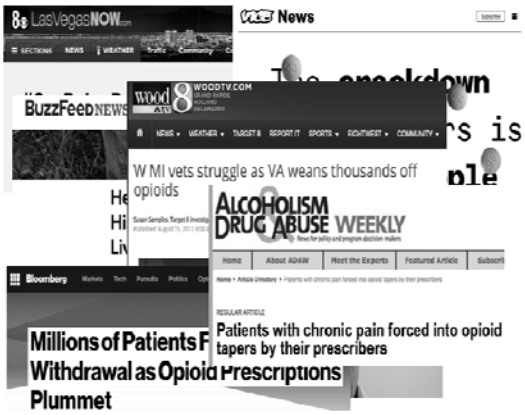
Interpretation of this Story

- Severe injuries, no clear fix, ever
- Long-term changes from alcohol use in remission (likely)
- Trauma induced dementia
- Iatrogenic harms
- Polypharmacy
- Opioid dependence
- Opioid pain relief
- Tenuous
- Taper would be high risk

Interpretation of this Story

- **Outcome**
- **Suicide with Ruger .44 purchased for this purpose by wife Meredith**
- **She held his hand as he shot himself through the chest**
- **Charged immediately**

"Think about how horrible it was to lose the person you love because the doctor has taken away the medication". "As much as I hated losing him, I understood why he made the choice better than anyone else could"

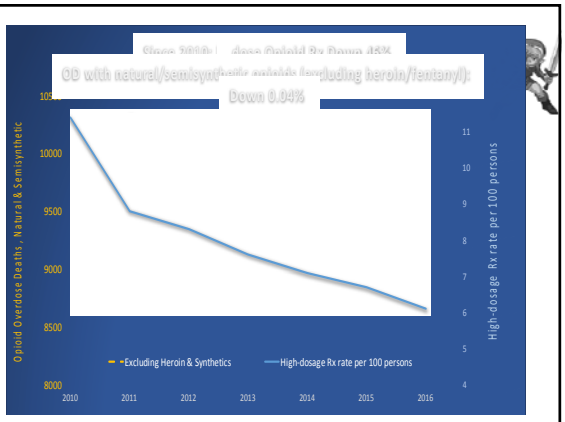


VA Data

Approved for Release, for the 2018 National Rx Drug Abuse & Heroin Summit

- Comparative analysis of Veterans discontinued vs continued (2 analyses: FY10-11 and FY 13-14)
- Patients prescribed <90 MME : 96% of sample and 86% of overdose suicide deaths
- Opioid discontinuation, compared to "continued"
  - **Increase** in suicide
  - **No decrease** in OD death (NS **increased**)
- Most discontinuations in VA are clinician-initiated

Has this happened elsewhere? **No one else has looked**



Conclusions

- **Prescribing contributed to today's problems**
- **There is a correction becoming overcorrection**
- **Opioids problematic, sometimes necessary**
- **Taper policies do not address most overdose risk (low dose)**
- **Unintended consequences**
  - **Patient: Out of pocket $, Abandonment, forced procedures, suicide**
  - **System: Project additional health system costs**
- **How many other areas of medicine do we do things to patients against their will with this level of evidence?**

EXTRA SLIDES

- My view
  - On average opioids don't outperform other options
  - I don't *think* doctors are routinely starting them when acetaminophen doesn't work
- There are situations we see that are more complicated than what was in this trial
- We need room/space to sort it out, sometimes including opioids

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

Table: Example medications within arms

	Opioid arm	Non-opioid arm
Step 1	Morphine IR*	Acetaminophen*
	Hydrocodone/APAP	Naproxen
Step 2	Morphine SR	Nortriptyline
	Oxycodone SA	Capsaicin topical
		Gabapentin
Step 3	Fentanyl transdermal	Tramadol

* Preferred initial medication selection

Deaths (excerp

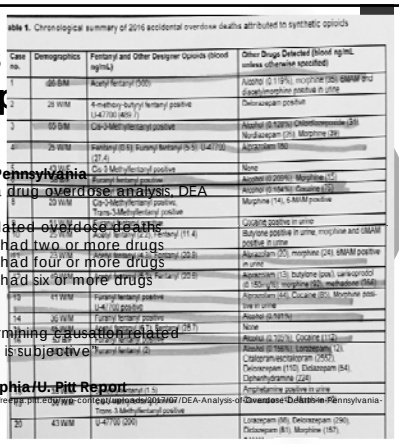


Table 1. Chronological summary of 2016 accidental overdose deaths attributed to synthetic opioids

OD Deaths, Pennsylvania
Pennsylvania drug overdose analysis. DEA

4642 drug-related overdose deaths
84% had two or more drugs
40% had four or more drugs
13% had six or more drugs

Limits: "determining causation related to overdoses is subjective."

DEA Philadelphia/U. Pitt Report
https://www.overdosefreepa.pitt.edu/wp-content/uploads/2017/07/DEA-Analysis-of-Overdose-Deaths-in-Pennsylvania-2016.pd_-1.pdf

TABLE 3. Opioid Prescription History Before Methadone and Other Opioid Poisonings

	n (%)		
	Methadone Poisonings (n = 798)	Other Opioid Poisonings (n = 1452)	P
Dose per day in week before event (mg/d MED)			<0.001
1–19	47 (5.9)	201 (13.8)	
20–49	30 (3.8)	203 (14.0)	
50–89	38 (4.8)	128 (8.8)	
90–119	16 (2.0)	59 (4.1)	
120–199	27 (3.4)	92 (6.3)	
≥200	171 (21.4)	151 (10.4)	
None in prior week	469 (58.8)	618 (42.6)	

70.4 % No or Low Dos

Washington Medicaid patients with an opioid Rx in 2006-2010, with ED or inpatient claim for opioid poisoning (Fulton-Kehoe, *Medical Care*, 2015

Dependence, Addiction reflect shades of grey!!