Putting Things Into Perspective: The U.S. Opioid “Crisis” and Pediatrics

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Tri-Cities Pain Conference

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Disclosures

I have received royalties for entries in UpToDate

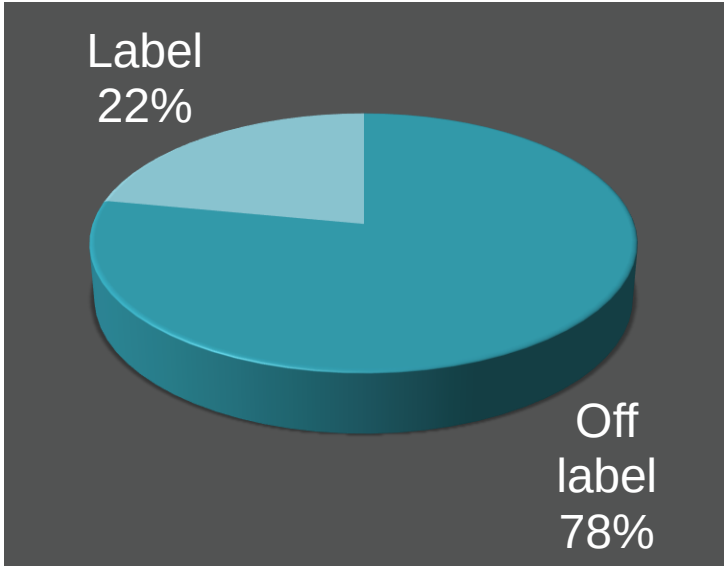
I will be discussing the off-label use of medications in pediatric populations

Objectives

- Learner will balance the pros and cons of using opioids to treat pain in pediatric patients
- Learner will evaluate data on the prevalence of opioid overdose deaths in the pediatric population
- Learner will differentiate issues of opioid misuse, opioid abuse, substance use disorder, and opioid-related overdose

Drug labeling for children in the U.S.

- Most medications used in pediatrics are not labeled for indications in children
- The tide is turning
- Analgesics have been slow to improve



https://www.fda.gov/drugs/information-consumers-and-patients-drugs/drug-research-and-children#:~:text=Pediatricians%20say%20it's%20about%20time,were%20labeled%20for%20pediatric%20use. Current through 5/4/2016

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Pediatrician prescribing

- 2 billion office visits studied
- 19 percent of the time, doctors ordered one or more off-label systemic drugs
- In visits with at least one drug order, doctors ordered drugs off-label
  - 83 percent of newborn visits
  - 49 percent of infant visits
  - 40 percent of visits for other ages
- Among visits with at least one ordered drug, rates of ordering off-label increased from 42 percent in 2006 to 47 percent by 2015

Hoon D, et al. Trends in Off-Label Drug Use in Ambulatory Settings: 2006-2015. Pediatrics. 2019 Oct;144(4):e20190896. doi: 10.1542/peds.2019-0896. Epub 2019 Sep 16. PMID: 31527173; PMCID: PMC7286122.

Per ChatGPT

"As of my last update in January 2022, approximately 50-60% of drugs prescribed to pediatric patients in the United States were off-label."

Pediatric drug development: The past

- Study of drugs in children was discouraged
  - Ethical issues
  - Fears of harming children
  - Perceived or real increased liability of testing drugs in children
- No incentives for drug companies to conduct pediatric trials
  - Relatively small market
  - Drugs will be used in children “off label”

For many drugs, limited or no data on

- Safety
  - Pharmacokinetics (PK)
  - Pharmacodynamics (PD)
  - Serious adverse events (SAE)
- Efficacy
- Dosing
- Long-term use
- Long-term sequelae

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The challenges: Physiology of pain

- Humans, especially very young ones, are developing rapidly but not at an identical pace
- Neurophysiology: The development of pain systems
- The costs of poorly treated pain are high
  - Peripheral sensitization
  - Central sensitization
  - Structural and functional changes

The challenges: Analgesics in the young

- Potential short- and long-term impact of analgesics
  - Pain system
  - More general neurophysiological development
  - Other organ systems
- Organ systems involved in pharmacokinetics are also developing
  - Liver
  - Kidney

BPCA and PREA

PREA

- Drugs and biologics
- Mandatory studies
- Requires studies only on indications under review
- Orphan indications exempt from study
- Pediatric studies must be labeled

BPCA

- Drugs and biologics
- Voluntary studies (6 months exclusivity)
- Studies relate to entire moiety and may expand indications
- Studies may be requested for orphan indications
- Pediatric studies must be labeled

Both revised and updated 5/2023

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Common drugs for pain in adults

- NSAIDs and acetaminophen
- Opioids
  - Few new drugs
  - Novel delivery methods, especially extended release
  - Abuse deterrent formulations
- Antidepressants (TCA, SNRI, SSRI)
- Antiepileptics
- Topicals

Problem (and an opportunity)

- Incentives and requirements for pediatric trials in place
- Pharma has been relatively adept at adult clinical trials
- Pediatric trials require different expertise
- Limited pediatric expertise in the Office of Anesthetics and Analgesics (now Office of Neuroscience - Division of Anesthesiology, Addiction Medicine, and Pain Medicine)
- Both FDA and pharma engaged pediatric experts

Defining some key points

- Ethical challenges
- Methodologic innovation
  - Present FDA Guidances
  - Placebo controlled studies
- Extrapolation (efficacy, safety)

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OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop

Charles B. Berde, Gary A. Walco, Elliot J. Krane, K. J. S. Anand, Jacob V. Aranda, Kenneth D. Craig, Carlton D. Dampier, Julia C. Finkel, Martin Grabois, Celeste Johnston, John Lantos, Alyssa Lebel, Lynne G. Maxwell, Patrick McGrath, Timothy F. Oberlander, Laura E. Schanberg, Bonnie Stevens, Anna Taddio, Carl L. von Baeyer, Myron Yaster and William T. Zempsky

Pediatrics 2012;129;354; originally published online January 16, 2012;
DOI: 10.1542/peds.2010-3591

Defining methods for acute pain

Comprehensive Review

PAIN®

Clinical trial designs and models for analgesic medications for acute pain in neonates, infants, toddlers, children, and adolescents: ACTTION recommendations

Gary A. Walco[a,b,*], Ernest A. Kopecky[c,d], Steven J. Weisman[e], Jennifer Stinson[f], Bonnie Stevens[f], Paul J. Desjardins[g], Charles B. Berde[h], Elliot J. Krane[i,j], Kanwaljeet J.S. Anand[k], Myron Yaster[l], Carlton D. Dampier[m], Robert H. Dworkin[n], Ian Gilron[o], Anne M. Lynn[a,b], Lynne G. Maxwell[p], Srinivasa Raja[l], Bernard Schachtel[q], Dennis C. Turk[a]

Day 1: Guidelines (published)
Day 2: Demonstration project (abandoned)

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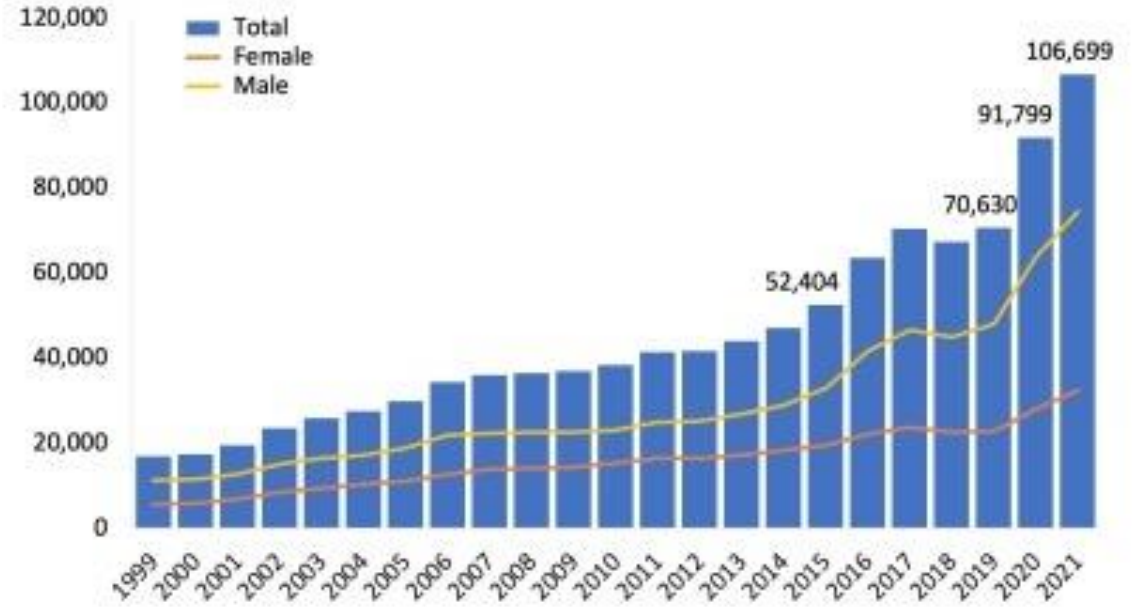
CDC data on overdose

The following 10 graphs come straight from the CDC, published June 30, 2023.

Source: https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates#:~:text=Opioid%2Dinvolved%20overdose%20deaths%20rose,(Source%3A%20CDC%20WONDER).

Figure 1. National Drug-Involved Overdose Deaths*, Number Among All Ages, by Gender, 1999-2021



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

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Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2021

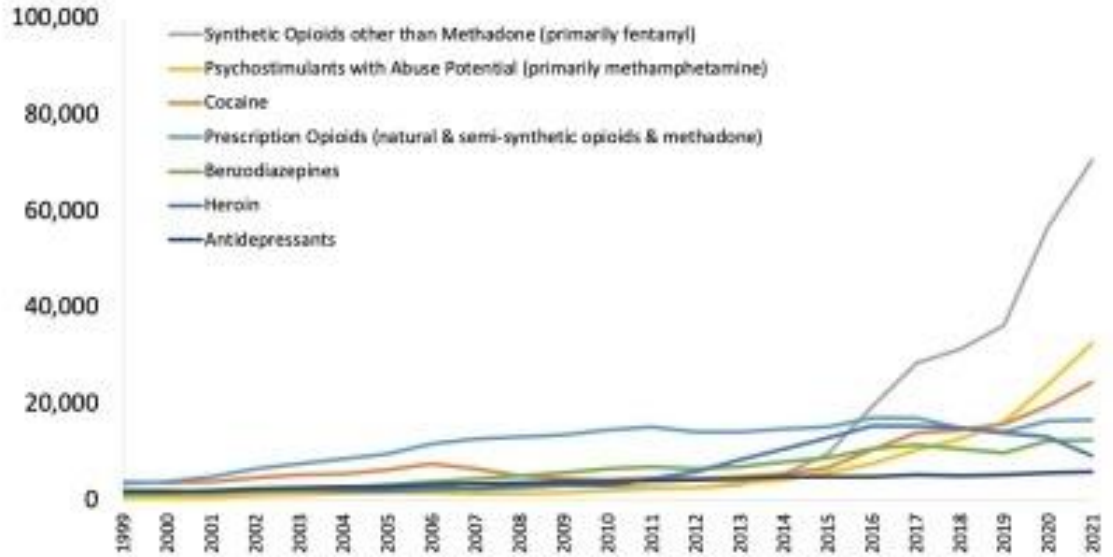

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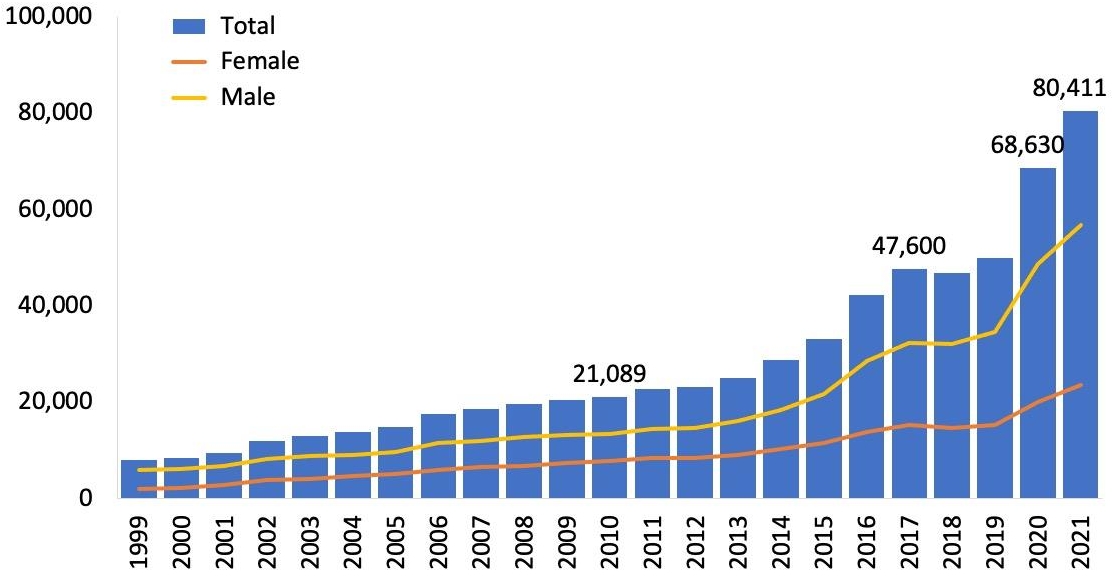
Figure 3. National Overdose Deaths Involving Any Opioid*, Number Among All Ages, by Gender, 1999-2021



*Among deaths with drug overdose as the underlying cause, the "any opioid" subcategory was determined by the following ICD-10 multiple cause-of-death codes: natural and semi-synthetic opioids (T40.2), methadone (T40.3), other synthetic opioids (other than methadone) (T40.4), or heroin (T40.1). Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

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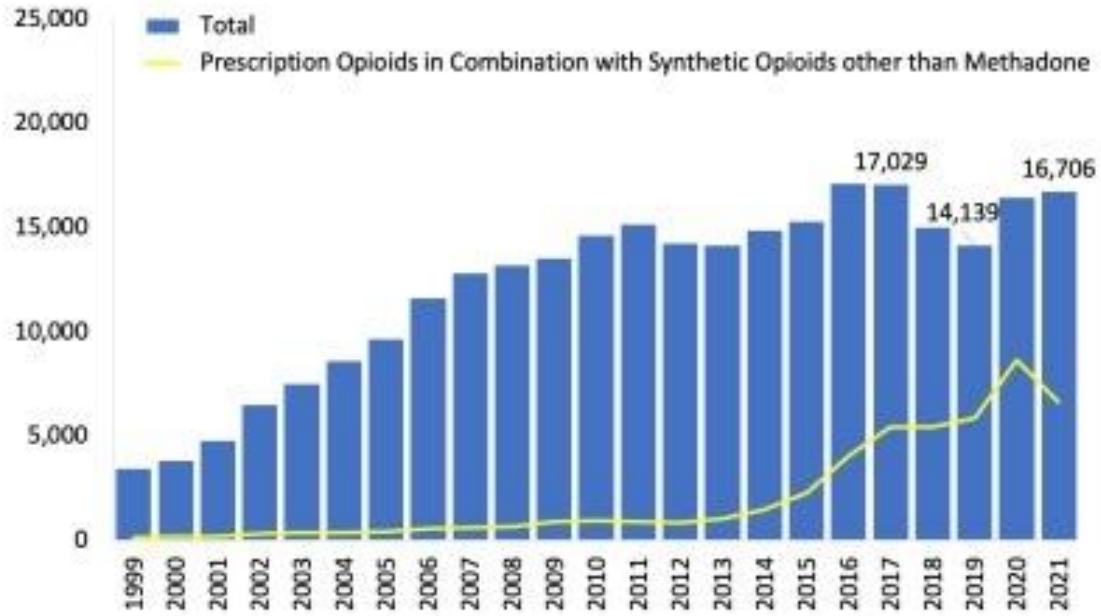
Figure 4. National Overdose Deaths Involving Prescription Opioids*, Number Among All Ages, 1999-2021



*Among deaths with drug overdose as the underlying cause, the prescription opioid subcategory was determined by the following ICD-10 multiple cause-of-death codes: natural and semi-synthetic opioids (T40.2) or methadone (T40.3). Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

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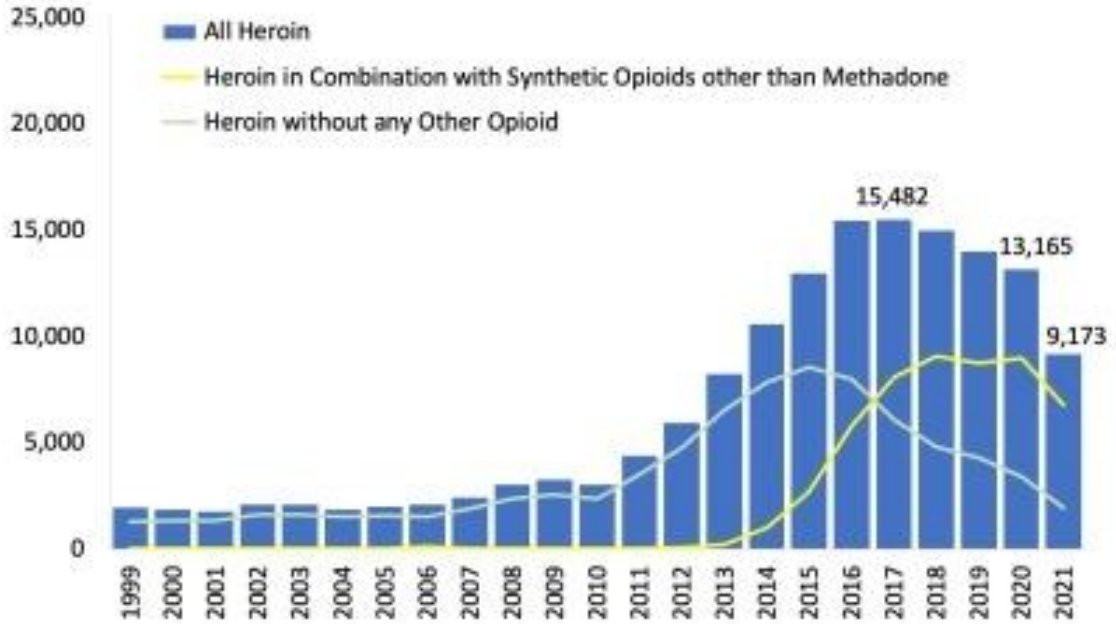
Figure 5. National Overdose Deaths Involving Heroin*, by other Opioid Involvement, Number Among All Ages, 1999-2021



*Among deaths with drug overdose as the underlying cause, the heroin category was determined by the T40.1 ICD-10 multiple cause-of-death code. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

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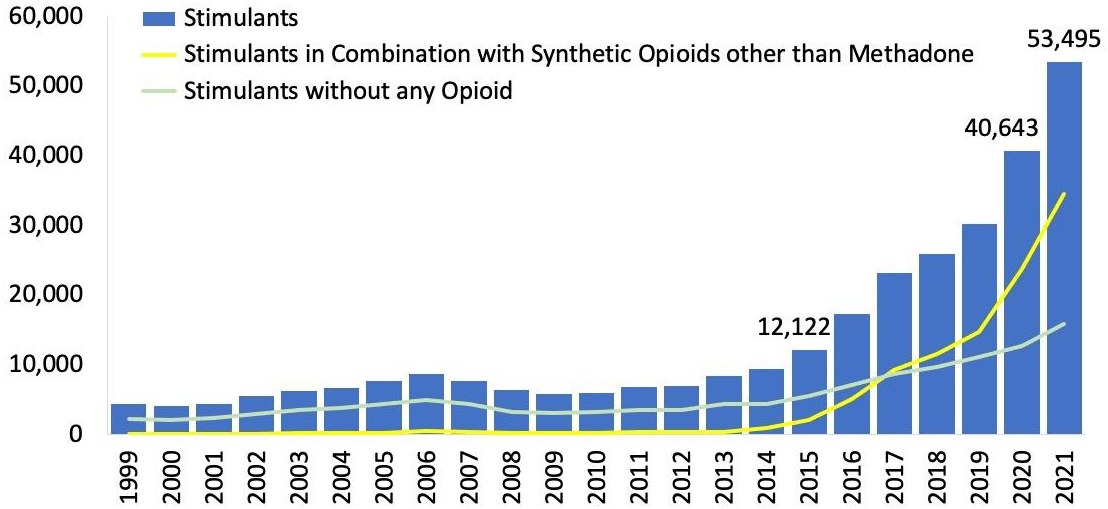
Figure 6. National Overdose Deaths Involving Stimulants (Cocaine and Psychostimulants*), by Opioid Involvement, Number Among All Ages, 1999-2021



*Among deaths with drug overdose as the underlying cause, the psychostimulants with abuse potential (primarily methamphetamine) category was determined by the T43.6 ICD-10 multiple cause-of-death code. Abbreviated to *psychostimulants* in the bar chart above. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

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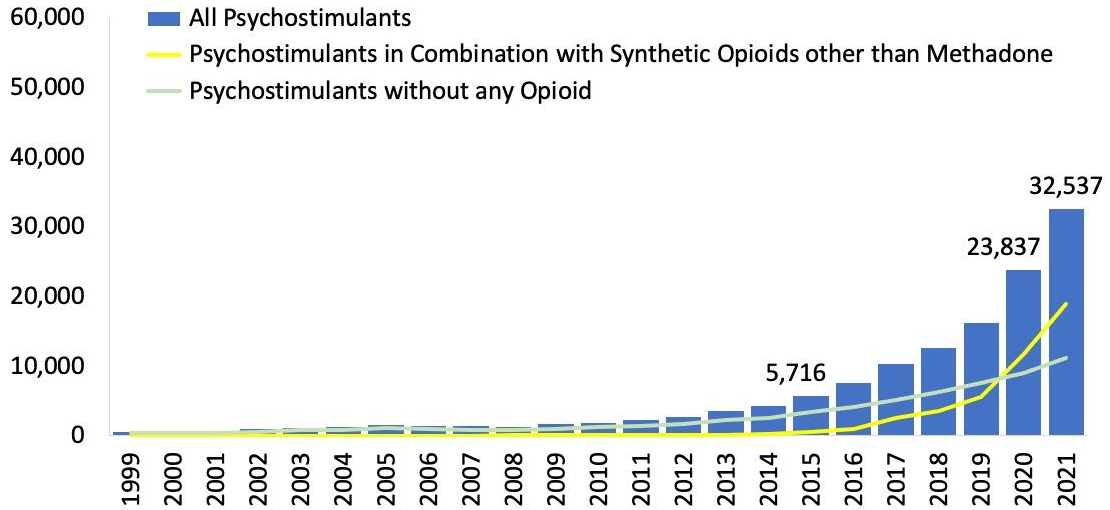
Figure 7. National Overdose Deaths Involving Psychostimulants with Abuse Potential (Primarily Methamphetamine)*, by Opioid Involvement, Number Among All Ages, 1999-2021



*Among deaths with drug overdose as the underlying cause, the psychostimulants with abuse potential (primarily methamphetamine) category was determined by the T43.6 ICD-10 multiple cause-of-death code. Abbreviated to *psychostimulants* in the bar chart above.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

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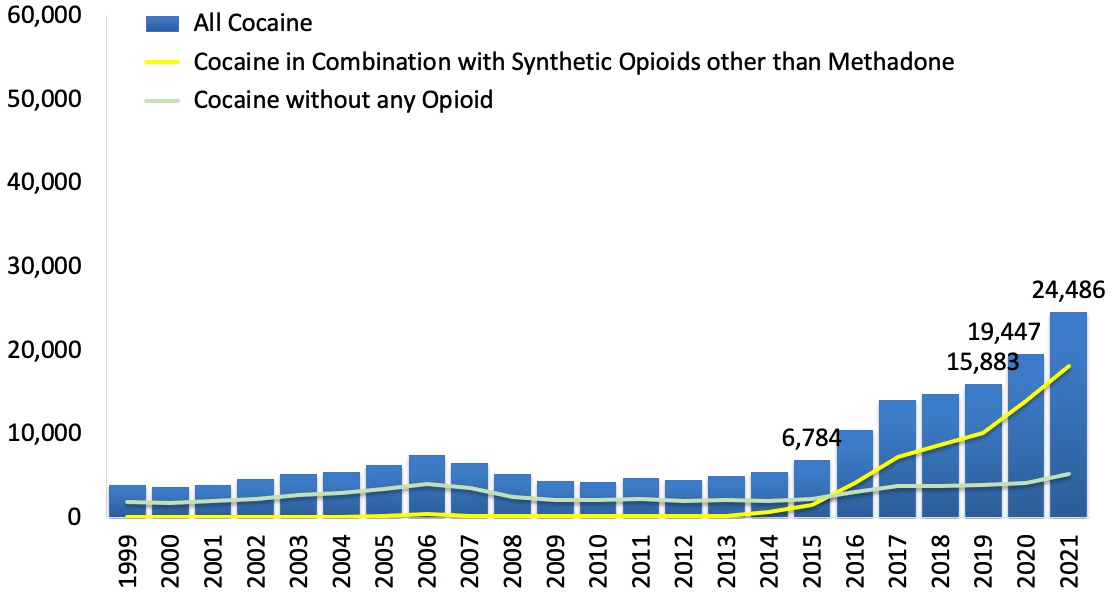
Figure 8. National Drug Overdose Deaths Involving Cocaine*, by Opioid Involvement, Number Among All Ages, 1999-2021



*Among deaths with drug overdose as the underlying cause, the cocaine category was determined by the T40.5 ICD-10 multiple cause-of-death code. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

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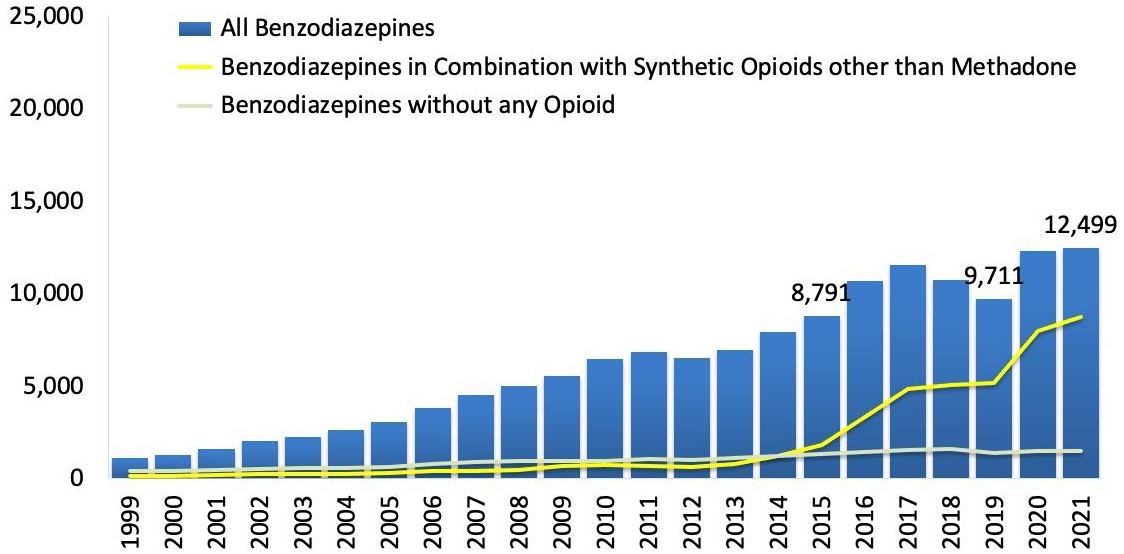
Figure 9. National Drug Overdose Deaths Involving Benzodiazepines*, by Opioid Involvement, Number Among All Ages, 1999-2021



*Among deaths with drug overdose as the underlying cause, the benzodiazepine category was determined by the T42.4 ICD-10 multiple cause-of-death code. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

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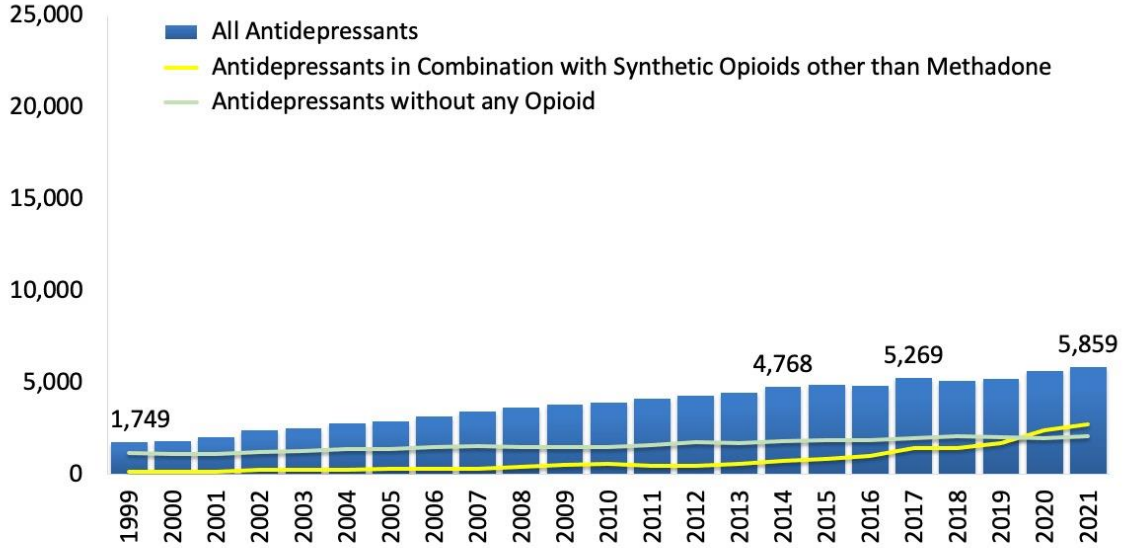
Figure 10. National Drug Overdose Deaths Involving Antidepressants*, by Opioid Involvement, Number Among All Ages, 1999-2021



*Among deaths with drug overdose as the underlying cause, the antidepressant subcategory was determined by the following ICD-10 multiple cause-of-death codes: Tricyclic and tetracyclic antidepressants (T43.0), monoamine-oxidase-inhibitor antidepressants (T43.1), and other unspecified antidepressants (T43.2). Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

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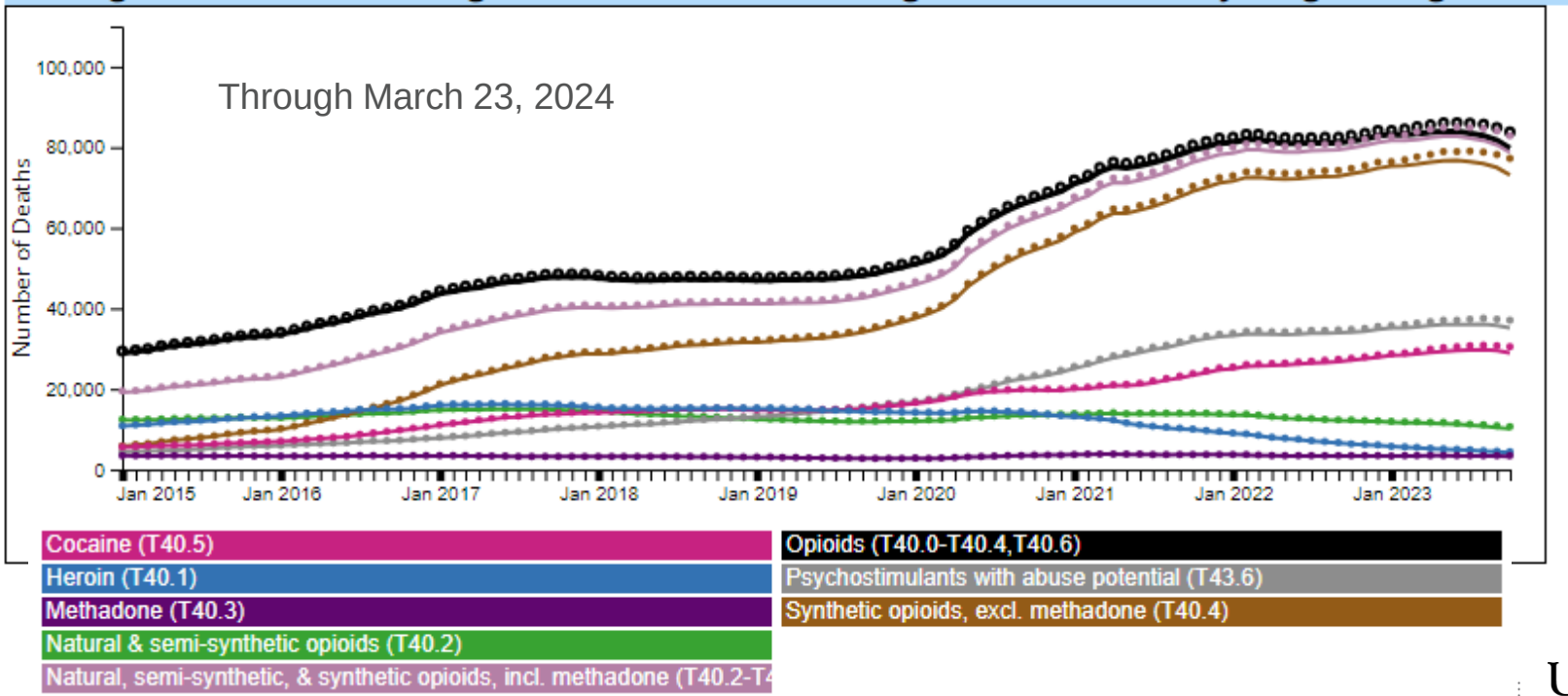
Are we improving?

Figure 2. 12 Month-ending Provisional Number of Drug Overdose Deaths by Drug or Drug Class: United States



All opioids
Synthetic opioids

Psychostimulants
Cocaine
Natural/synthetic opioids
Heroin
Methadone

https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

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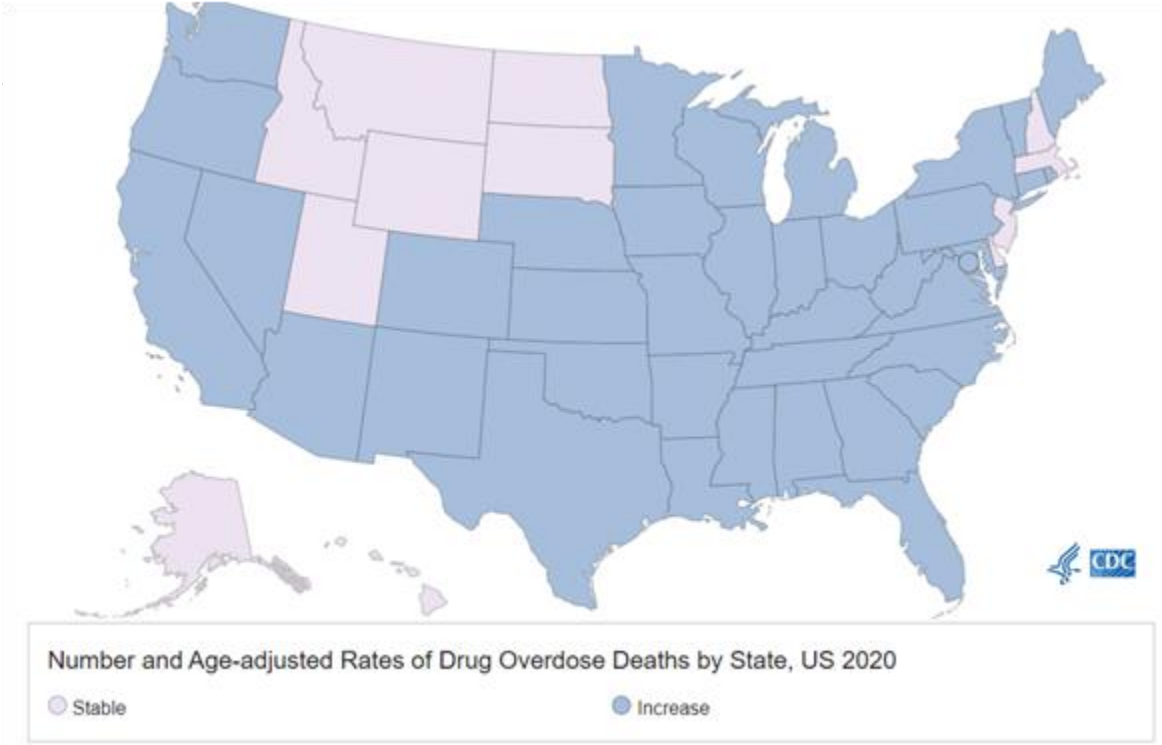

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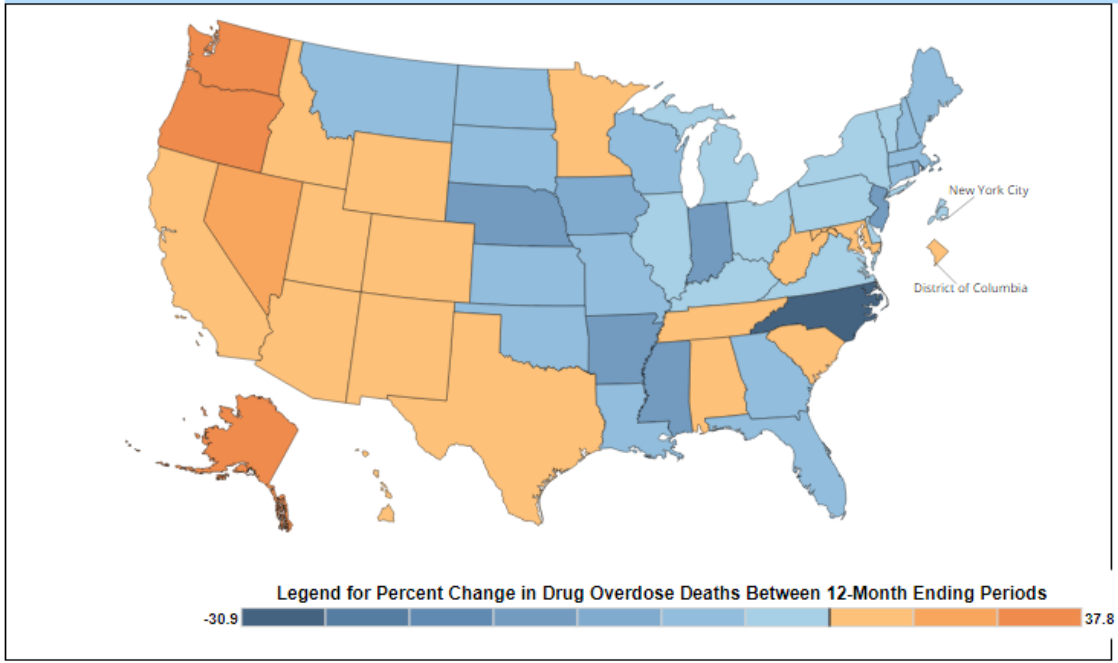
Are we improving?

Figure 1b. Percent Change in Reported 12 Month-ending Count of Drug Overdose Deaths, by Jurisdiction: October 2022 to October 2023



Select predicted or reported number of deaths

- Predicted
- Reported

Percent Change for United States

-2.3

https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

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A major problem: Synthetic opioids

- Fentanyl is ~100x the potency of morphine
- 2 milligrams of fentanyl can be lethal depending on body size, tolerance and past usage
- DEA analysis of counterfeit pills: range from 0.02 to 5.1 milligrams of fentanyl per tablet
- 42% of pills tested for fentanyl contained at least 2 mg of fentanyl, considered a potentially lethal dose
- Street cost of fentanyl: as low as 50¢ to $1.00 per tablet

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10332699/#app3-jetem-7-3-l1

If “prescription opioids” are the problem…

- Limit prescribing
  - Federal
  - State
  - Institutional
- Pediatric populations deemed to be at greater risk
  - More severe limitations placed on prescribing to children and adolescents
  - “If you prescribe an opioid to an adolescent, there is a fairly good chance they will become an addict.”

A new spin on NNH

- Number Needed to Harm (NNH): The number of people who, if they received the intervention in question, would lead to just one person being harmed.
- Number Needed to Undertreat: ***How many legitimate patients will be under- or untreated in order that one less person becomes addicted to opioids?*** (Carr, 2016)

Weighing out the probabilities of two harms

Prescribing an opioid for acute pain will lead to substance abuse or overdose of:

- that patient
- someone remote

Undertreated pain will lead to

- Increased sensitivity to pain
- Chronic pain syndromes
- Psychological concerns

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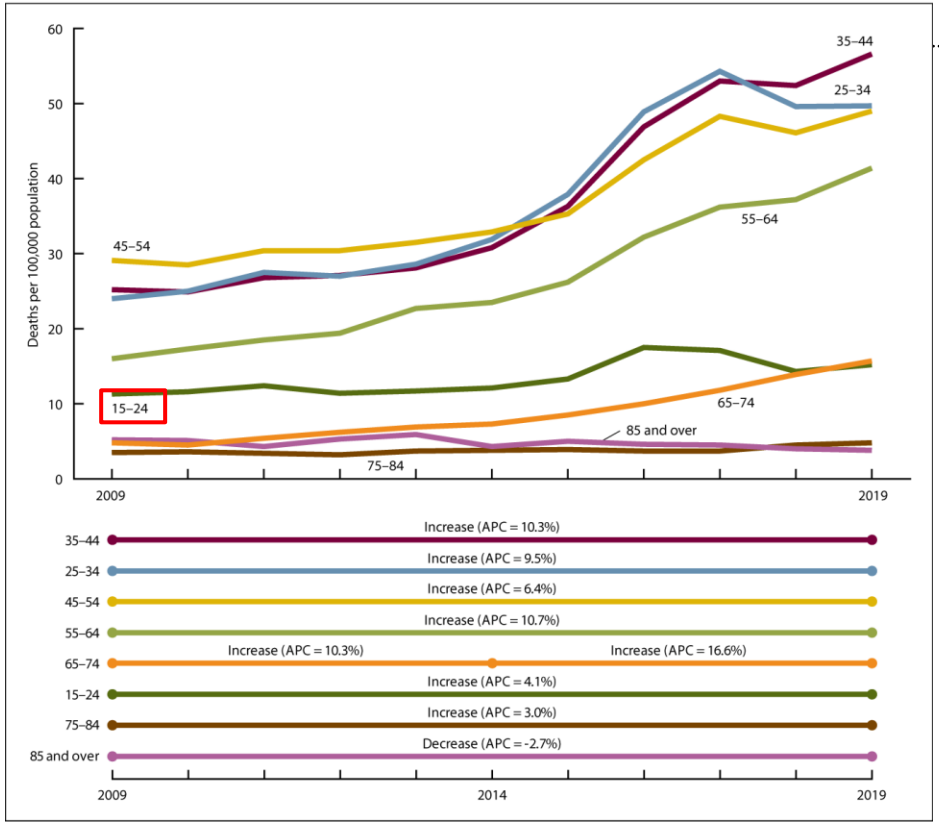
Drug overdose death rates by age

Figure 2. Drug overdose death rates among males aged 15 years and over, by age group: United States, 2009–2019



Key notes:

- No data <15 years
- Among males, the age-adjusted drug overdose death rate increased from 14.8 per 100,000 in 2009 to 29.6 in 2019.
- Among females, the age-adjusted drug overdose death rate increased from 9.1 per 100,000 in 2009 to 13.7 in 2019.

https://www.cdc.gov/nchs/hus/topics/drug-overdose-deaths.htm#featured-charts

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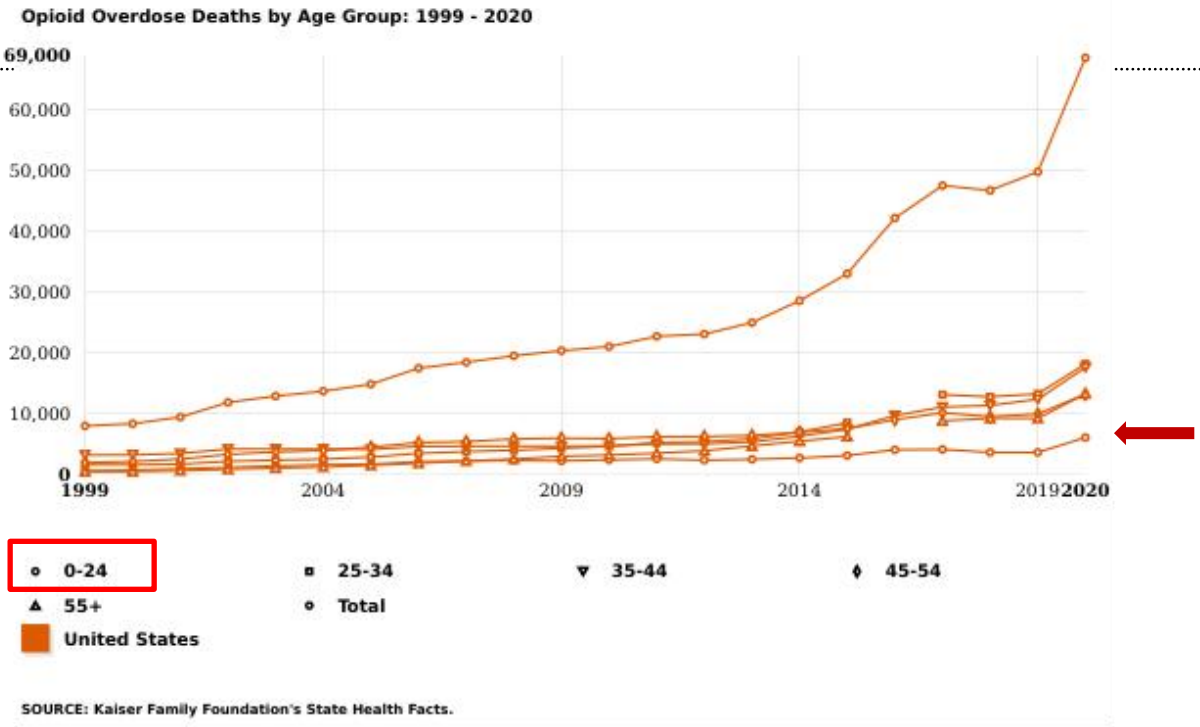
Opioid overdose deaths by age group

Is 0 to 24 years a meaningful grouping?



https://www.kff.org/other/state-indicator/opioid-overdose-deaths-by-age-group/?activeTab=graph&currentTimeframe=0&startTimeframe=21&selectedRows=%7B%22wrapups%22:%7B%22united-states%22:%7B%7D%7D%7D&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D

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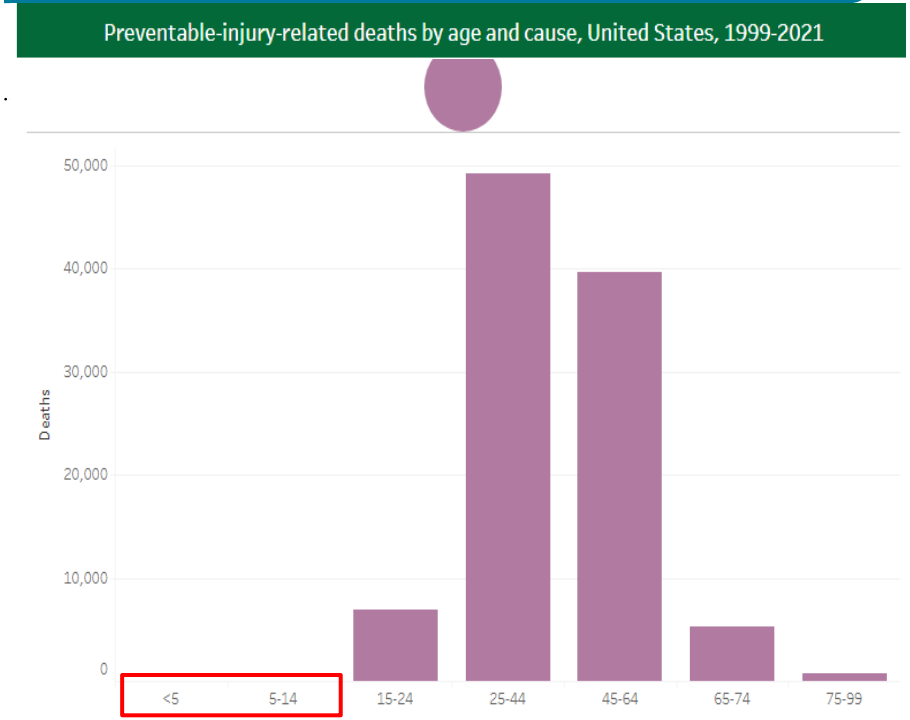
Opioid overdose deaths by age group



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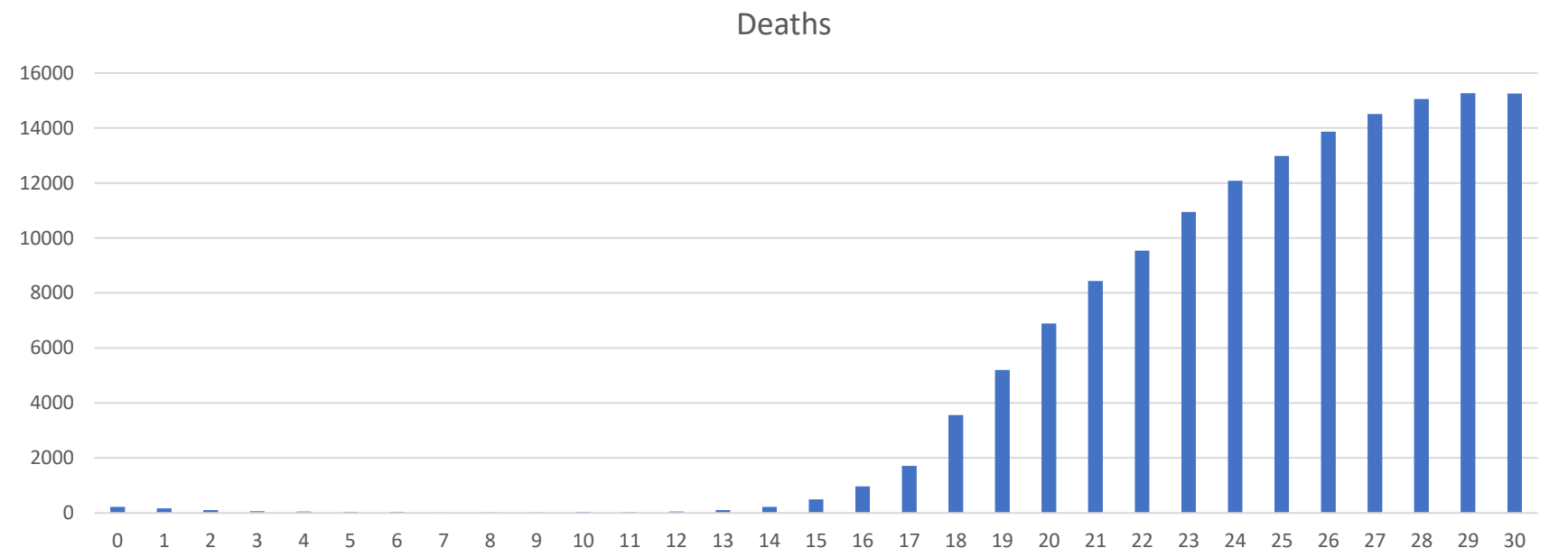
Injuryfacts.nsc.org

Unintentional drug overdose deaths by age (1999-2019)



https://wonder.cdc.gov/controller/datarequest/D77;jsessionid=17756312EF3C5FEBBC0B576F62EE

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How commonly are opioids prescribed to children?

2016	# prescriptions	Rate (per 100K)
All ages	61,862,364	19.1
0-14	1,235,397	2.0
15-19	2,456,537	11.6
0-19	3,691,934	

- 2020 US Census data: 22.1% of population was under 18 years (down from ~24% in 2010)
- People under 18 get 5.96% of opioids

Source: QuintilesIMS® Transactional Data Warehouse

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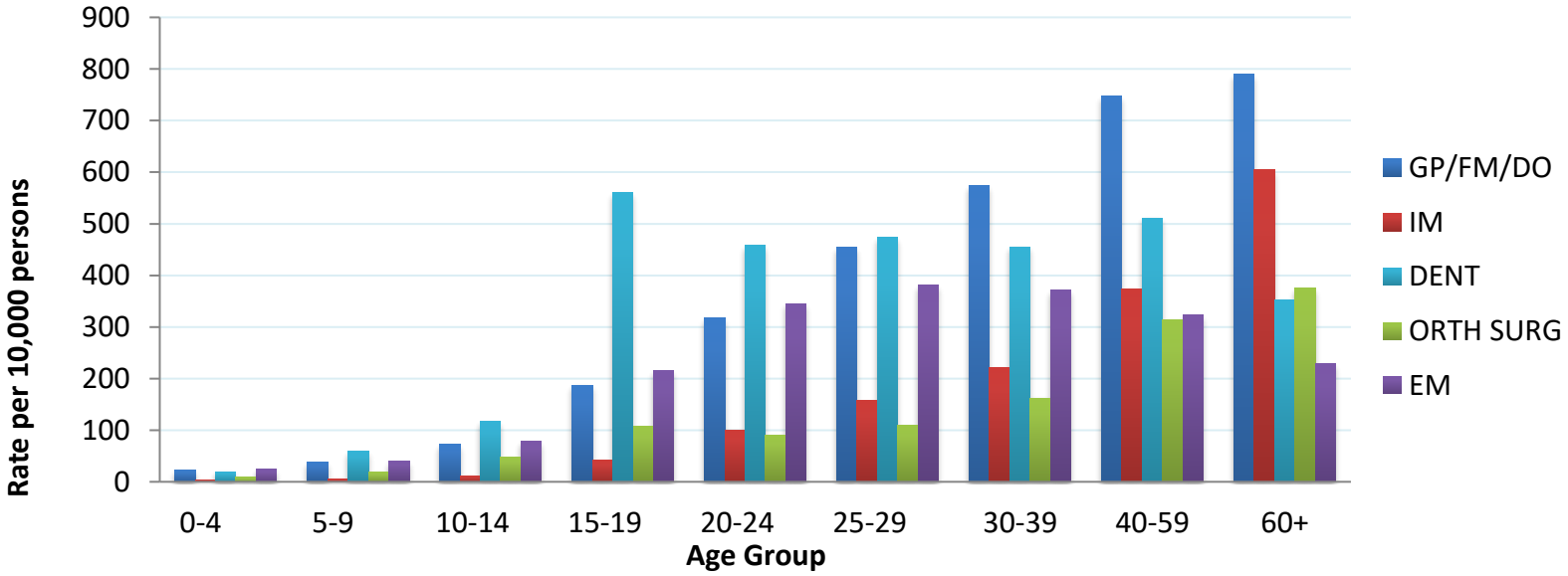
Who is prescribing?



IMS Vector ®One National, TPT 06-30-10 Opioids Rate 2009

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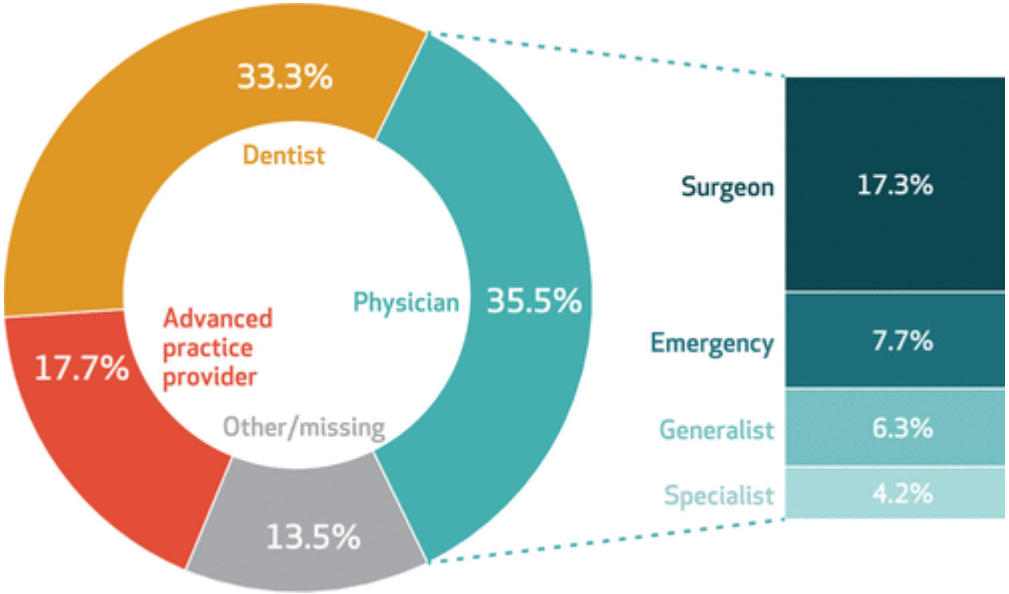
More recent data (NC, 2016-2018)



https://doi.org/10.1377/hlthaff.2020.00724

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Are prescribers' practices improving?

- 4 027 701 outpatient prescriptions (2019)
- 3.5% of US children and young adults (0 to 21 years) had ≥1 dispensed opioid prescription
- For opioid-naive patients:
  - 41.8% exceeded a 3-day supply
  - 3.8% exceeded a 7-day supply
  - For young children, 8.4% were for codeine and 7.7% were for tramadol

Chua, Kao-Ping, et al. "Opioid prescribing to US children and young adults in 2019." Pediatrics 148.3 (2021).

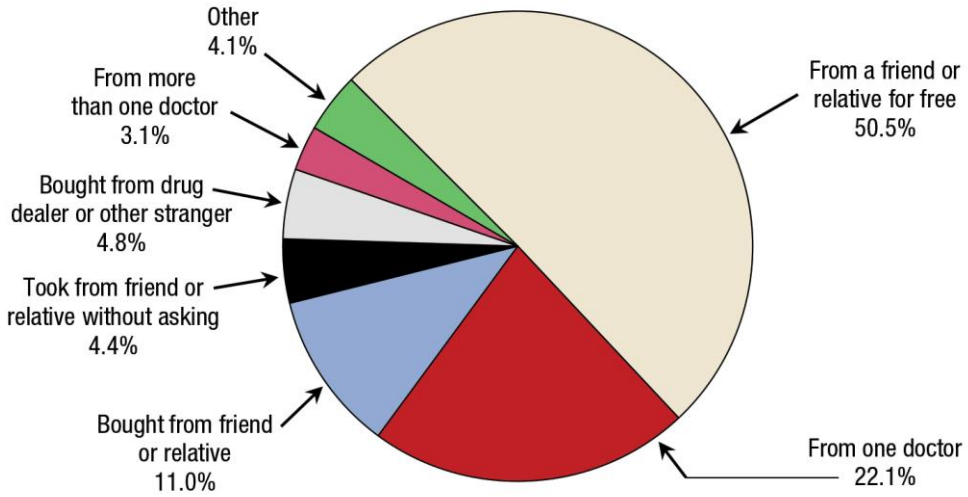
Are providers improving?

- For adolescents and young adults:
  - 11.5% had daily dosages of ≥50 morphine milligram equivalents
  - 4.6% had benzodiazepine overlap
- Overall, 45.6% of prescriptions were high risk by ≥1 metric
- Dentists and surgeons wrote 61.4% of prescriptions
- High-volume prescribers (95th percentile) wrote 53.3% of prescriptions and 53.1% of high-risk prescriptions

Define some terms: They are not interchangeable

- Opioid misuse
- Nonmedical use of opioids
- Opioid abuse
- Substance Use Disorder
- Accidental death from opioid overdose
- All deaths from opioid overdose (includes suicide and homicide)

Source of prescription pain relievers for the most recent nonmedical use among past year users aged 12 or older



SAMHSA, Center for Behavioral Health Statistics and Quality,
National Surveys on Drug Use and Health (NSDUHs), 2013 and 2014.

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Sources of pharmaceutical opioids for nonmedical use

- N=390 18–23-year-olds in Columbus, Ohio
- Self-report non-medical use of pharmaceutical opioids on at least 5 occasions in the past 90 days
- No lifetime dependence on opioids based on DSM-IV criteria
- No history of heroin use or drug injection
- Not engaged in a formal drug abuse treatment program in the last 30 days
- Express intention to use non-prescribed pharmaceutical opioids again
- Not currently be awaiting trial or have pending criminal charges

Source	Ever (select all that apply)	In the past 6 months (select the most common source)
Own prescription	184 (47.2%)	15 (3.8%)
Given free by friends	343 (87.9%)	114 (29.2%)
Given free by relatives	173 (44.4%)	44 (11.3%)
Bought	314 (80.5%)	210 (53.8%)
Took from relatives	80 (20.5%)	4 (1%)
Took from friends	42 (10.6%)	0
Doctor shopping	43 (11.0%)	2 (0.5%)
Internet	3 (0.8%)	0
Other	1 (0.3%)	1 (0.3%)

Daniulaityte R et al. Sources of pharmaceutical opioids for non-medical use among young adults. J Psychoactive Drugs. 2014 ; 46(3): 198–207

Issues to consider

- Major source of prescription drugs for misuse are those available in medicine chests (overprescribing)
- How many parents will hand a bottle of prescription opioids to their child or adolescent to take on their own?...but also rarely locked up
- What other “dangerous” drugs are children given regularly?
  - Psychostimulants
  - OTC analgesics, antihistamines

Temporal aspect of pain

Acute Pain

- Clear onset, relatively clear offset
- Typically tied to known pathophysiology
- Goal of medication treatment: Eradicate the pain until condition heals, weighing risks and benefits

Chronic Pain

- Onset is unclear, no specified offset
- Degree of known pathophysiology is variable
- Goal of medication treatment: Reduce pain intensity, frequency, and duration to the degree possible, weighing risks and benefits

Opioid sparing strategies for acute pain

- **Children suffering needless pain is not an option**
- Currently, with its flaws, there are no better drugs available to treat moderate to severe acute pain
- Methods to reduce amounts of opioid used?
  - Acetaminophen and NSAIDs
  - Regional anesthesia
  - Adjuvant medications (e.g., antiepileptics)?
  - Dexmedetomidine?
  - Ketamine?
  - Other opioids (e.g., methadone)?
  - Lidocaine infusions?

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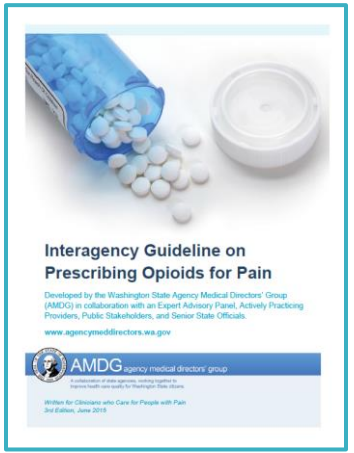
Opioids for chronic pain in pediatrics

- Available data indicate the opioid therapy for chronic pain in children and adolescents is far less common than in adults
- Guidelines define criteria to do so:
  - Known organic pathology
  - Defining an endpoint (sometimes challenging)
  - Using as little as necessary to achieve goals
  - Formal assessment of abuse potential



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Analgesics with pediatric indications for pain (US) through 8/2023

Studied and approved

- Morphine (0+ years)
- Diclofenac (12+ years)
- Duloxetine (FMS; 13+ years)
- Acetaminophen (2+ years)
- Ibuprofen (6+ months)
- OxyContin (11+ years)
- Fentanyl patch (2+ years)
- Aspirin (2+ years)
- Tapentadol (6+ years)

Studied and not approved

- Acetaminophen IV (0 to 2 years)
- Oxycodone
- Buprenorphine
- Pregabalin (for pain)
- Salonpas
- Fentanyl lozenge
- Gabapentin
- Hydromorphone
- Methadone
- Tramadol

https://www.fda.gov/science-research/pediatrics/pediatric-labeling-changes

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Other medications for chronic pain

- Adult chronic pain syndromes are a function of aging and often neuropathic in nature
  - Diabetic neuropathy
  - Post-herpetic neuralgia
  - Osteoarthritis
  - Radiculopathy
- Medications are tested in these populations
- Can we extrapolate to chronic pain in pediatrics?

Analgesic medications without labeling for pediatric use

NSAIDs

- Ketorolac
- Diclofenac
- Fenprofen
- Flurbiprofen
- Ketoprofen
- Nabumetone
- Piroxicam
- Sulindac

Opioids

- Hydrocodone ER
- Hydromorphone
- Methadone
- Oxycodone IR
- Oxymorphone
- Tramadol
- Nalbuphine
- Butorphanol
- Levorphanol
- Pentazocine

Combination products

- Hydrocodone/ibuprofen
- Oxycodone/APAP
- Oxycodone/ASA
- Tramadol/APAP

Where do we go from here?

- New moieties to treat acute and chronic pain
- Helping to End Addiction Long-term (HEAL) Initiative: analgesic development is being fast-tracked
- BPCA and PREA, with their updates
- Data on current usage, effectiveness, adverse reactions are generally absent
- Longitudinal studies are optimal

Thank you

Old Buddhist saying:

“Pain is inevitable; suffering is optional.”