

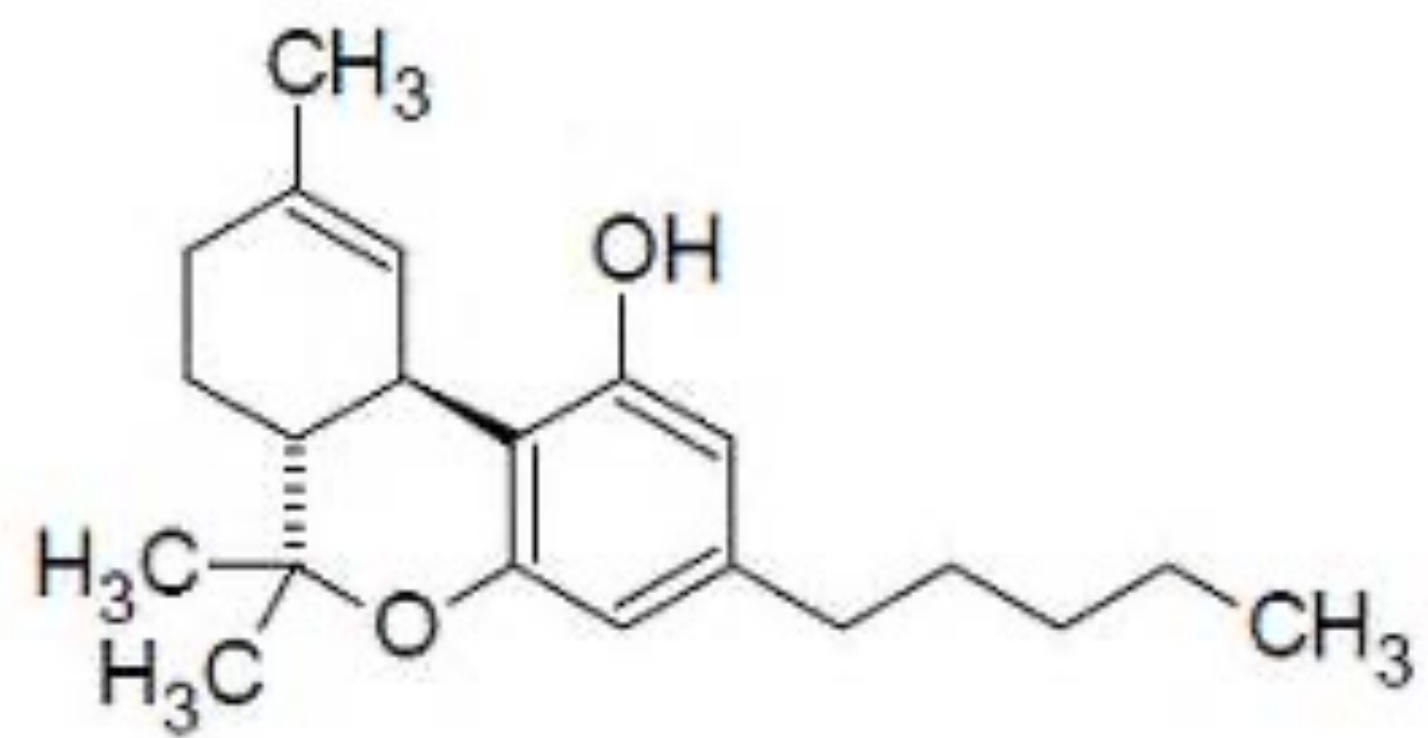
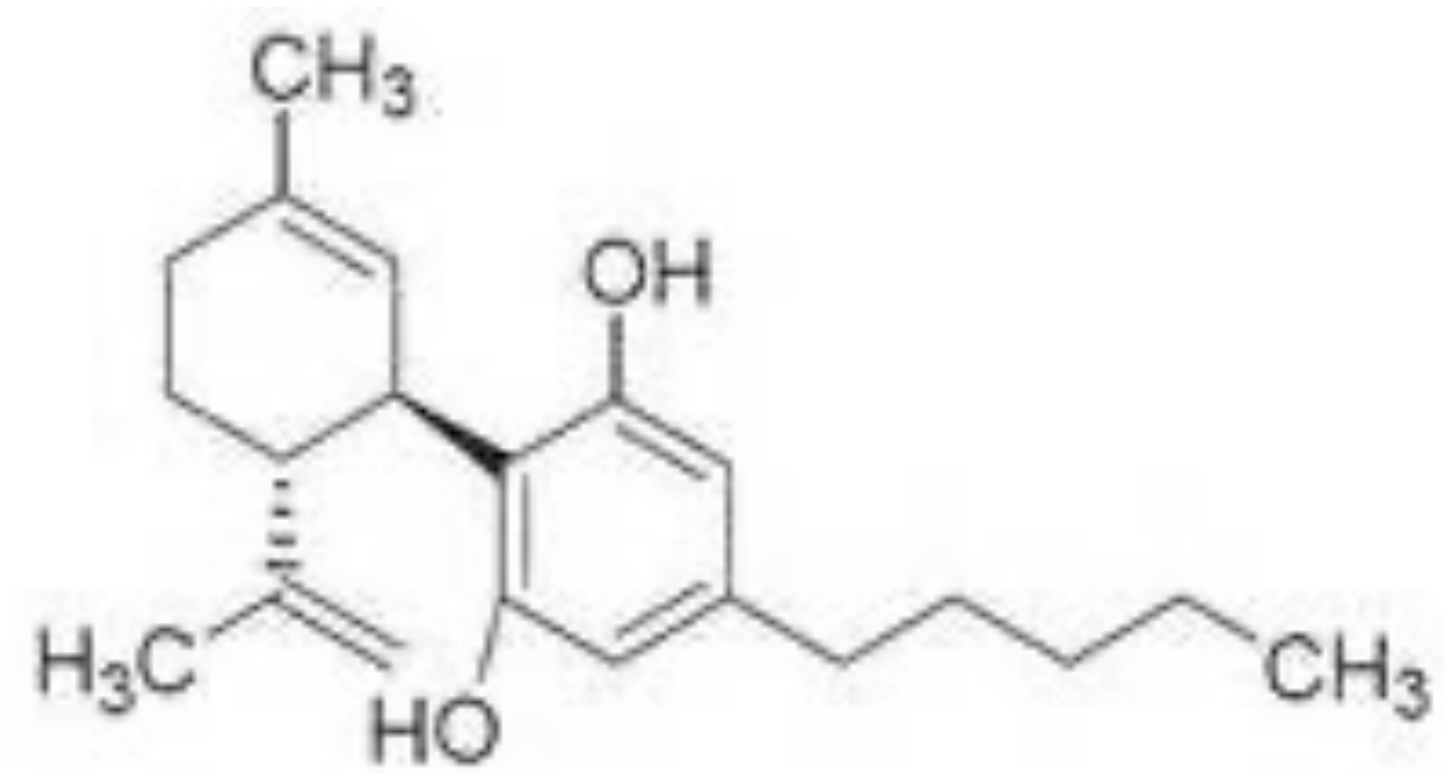
Cannabis and the Opioid Connection

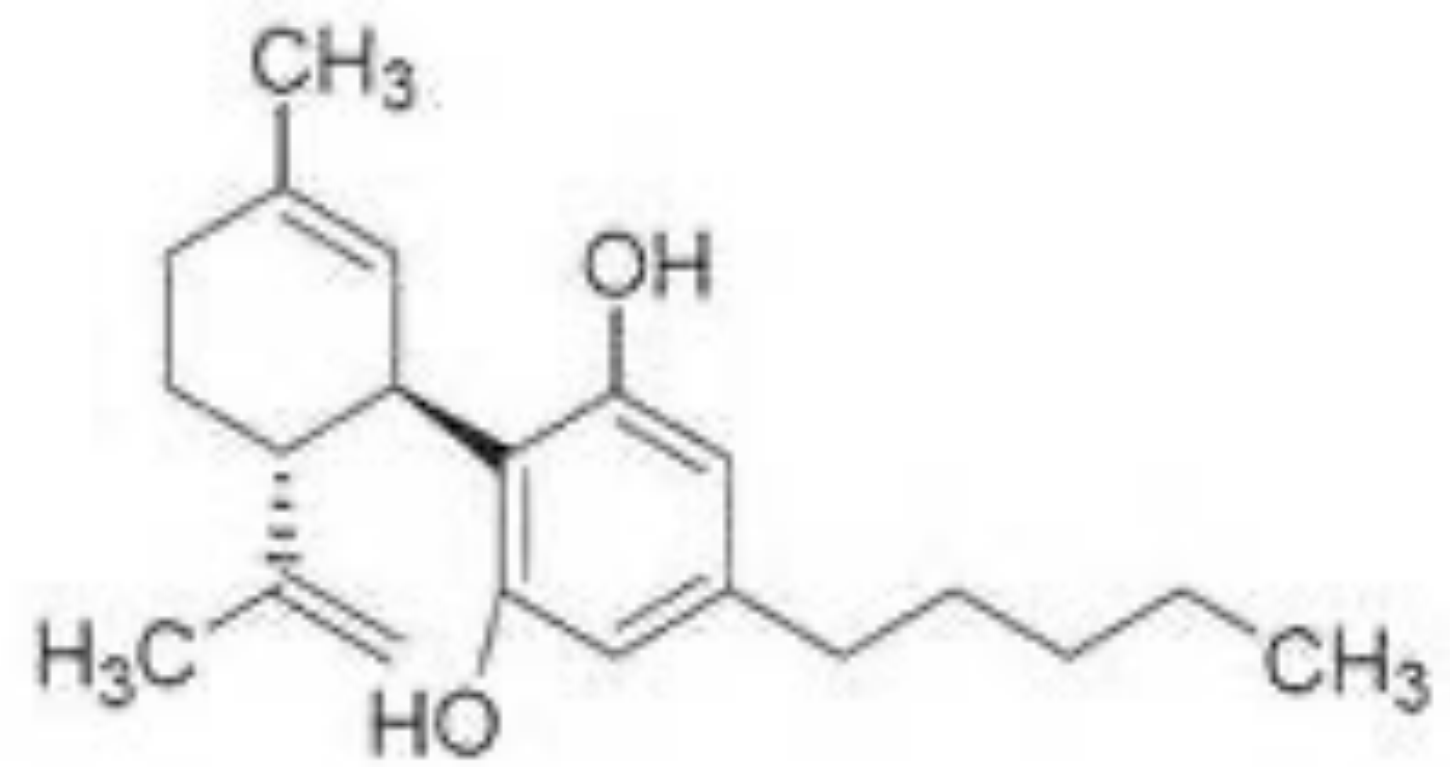
Kenneth Finn, MD

kfinn@springsrehab.net

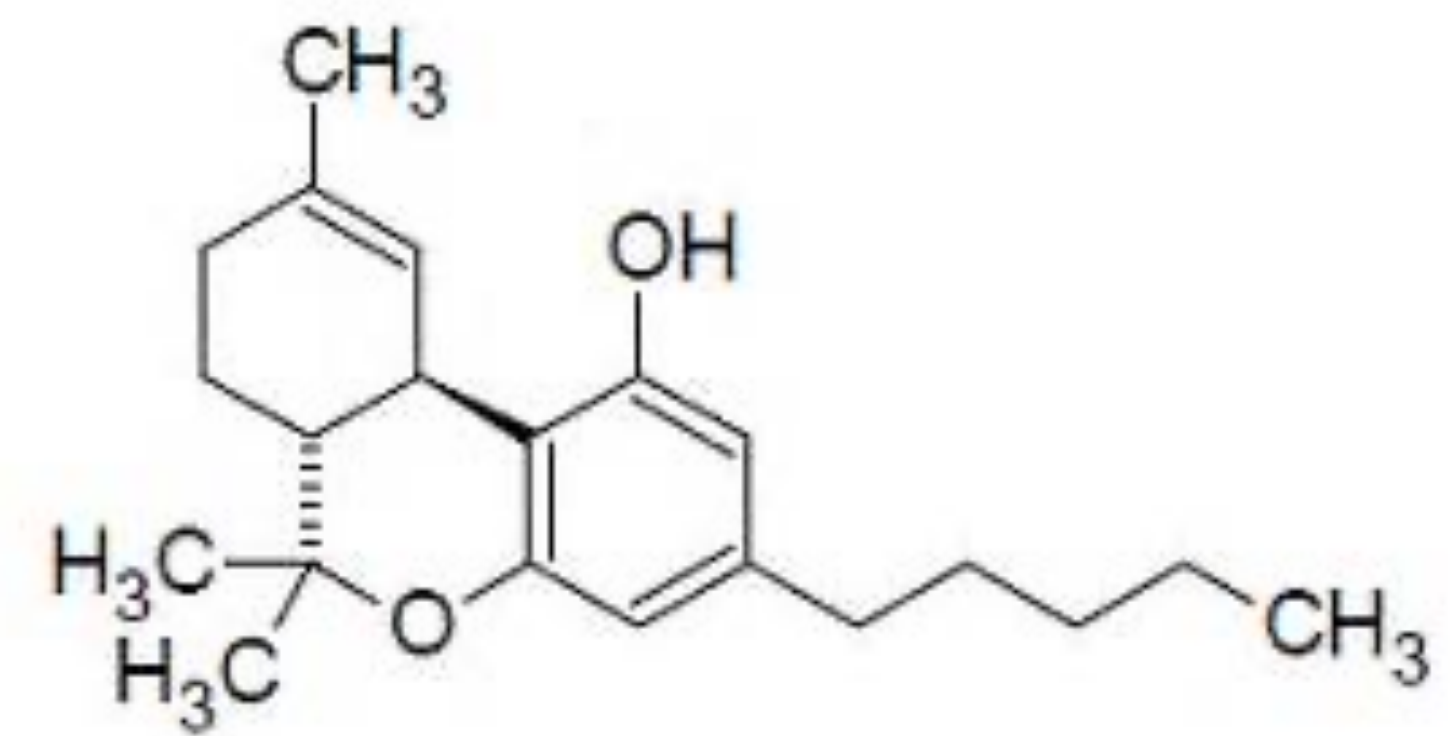
Disclosure

- Honoraria for speaking
- Royalties: Cannabis in Medicine: An Evidence-Based Approach

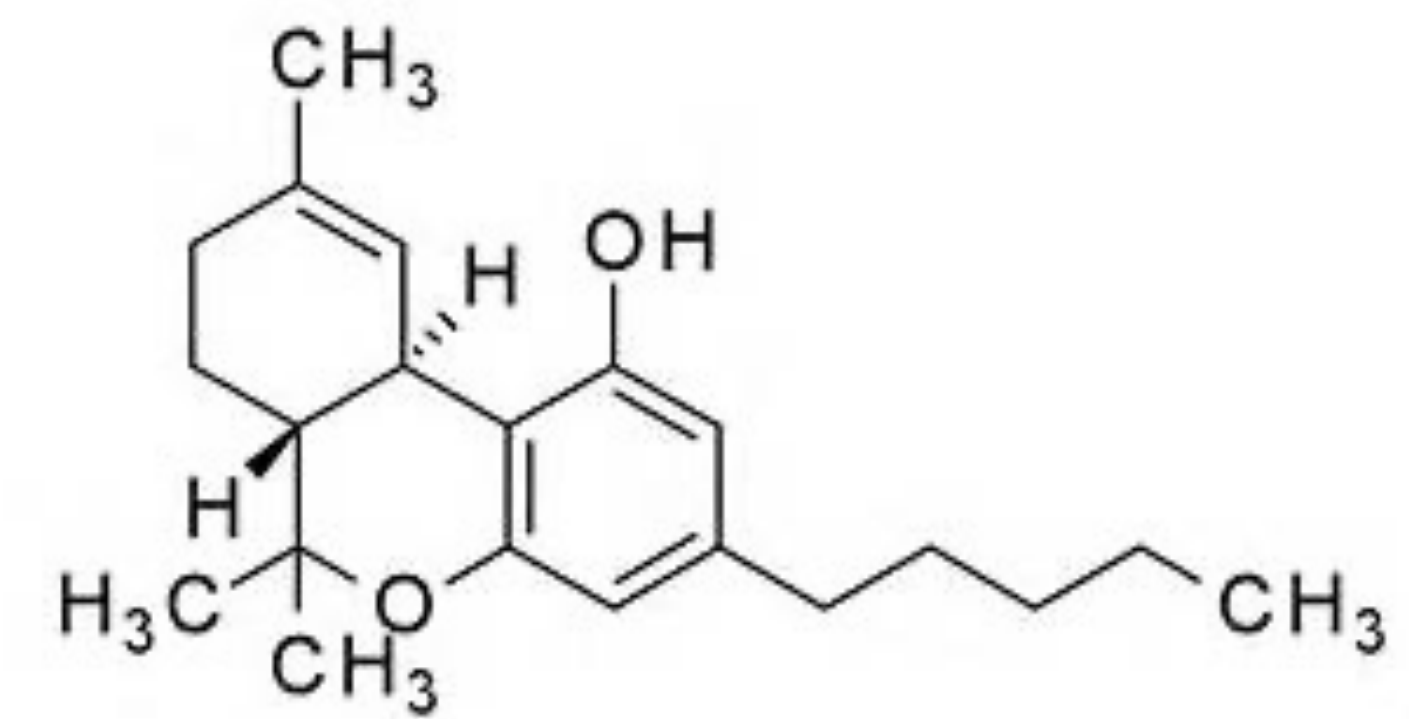




CBD



Dronabinol



THC



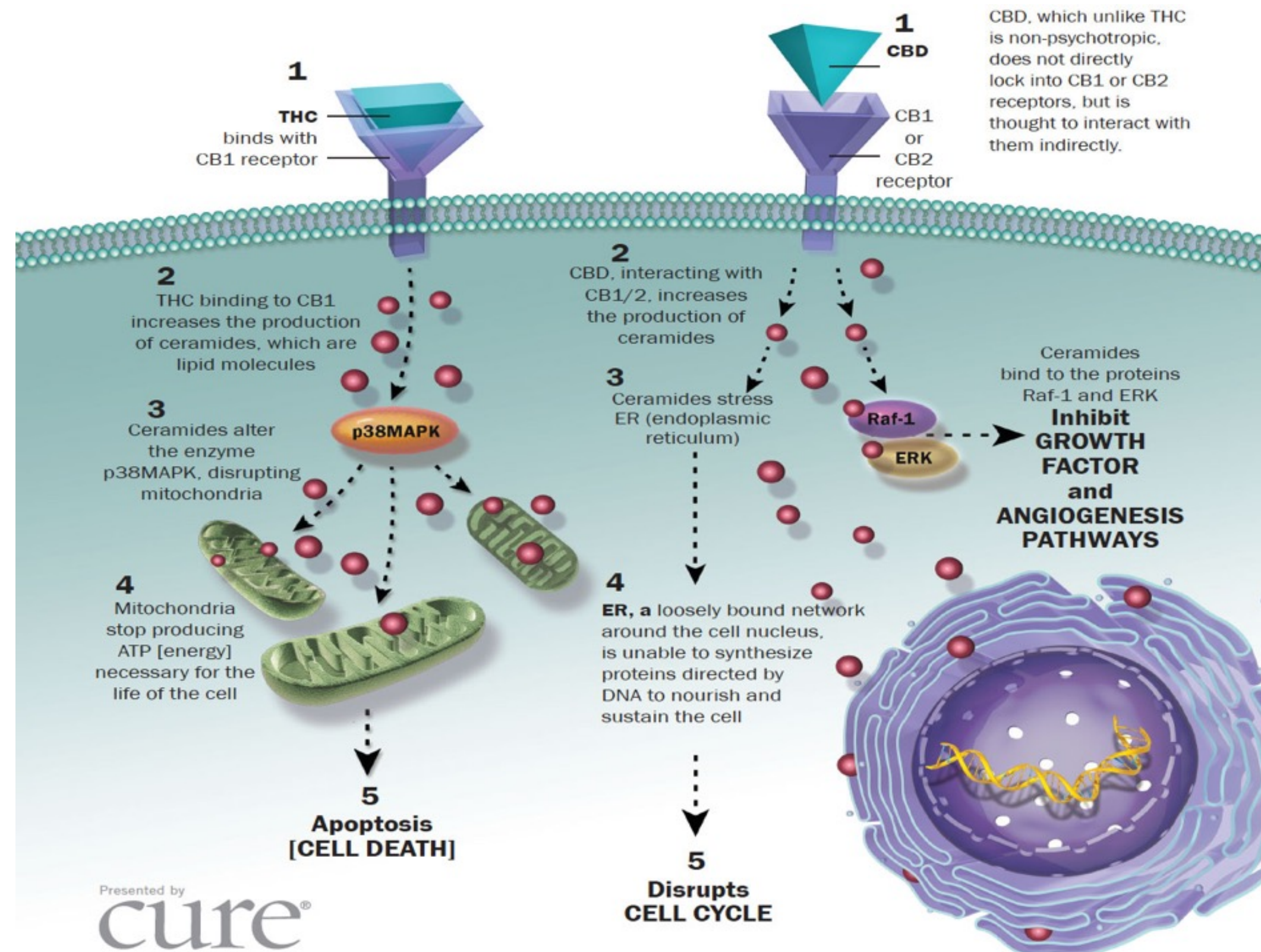
Terminology

- Cannabis-based medication
 - Registered medicinal cannabis extracts with defined and standardized THC and THC/CBD content should be classified as ‘cannabis-derived’ or ‘cannabis-based’ medicines.
 - Examples: Epidiolex®, Sativex ®(natural); dronabinol (semi-synthetic); nabilone (synthetic)
- Medical cannabis
 - Cannabis plants and plant material, for example flowers, marijuana, hashish, buds, leaves or full plant extracts used for medical reasons.
 - Poorly regulated and poorly tested for contaminants

National Ambulatory Care Survey, 2018

- National Survey
- Why people see their doctor
- **Knee pain** the only pain diagnosis in top 20 reasons
- Others **not** in top 20: Back pain, Shoulder pain, Neck pain, Neuropathy, Headache, Fibromyalgia, Cancer, Seizure, other
- https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2018-namcs-web-tables-508.pdf

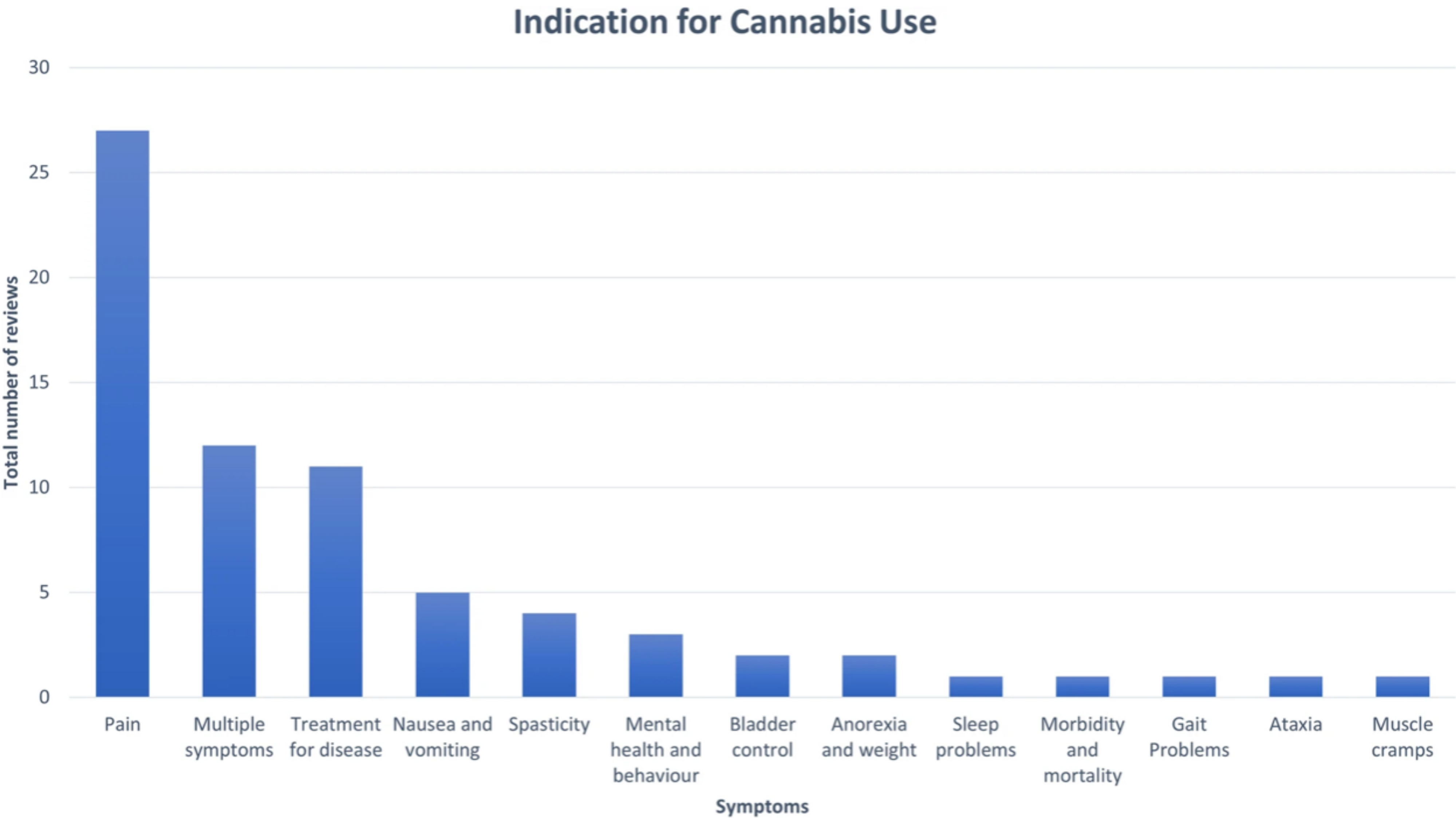
Cannabis and Opioid Relationship




- Synergistic systems
- Both belong to the rhodopsin subfamily of G-protein coupled receptors
- Both, when activated, reduce cellular levels of cyclic adenosine monophosphate (**cAMP**) by inhibiting adenylyl cyclase

Cannabis and Opioid Relationship

- Both receptors found at presynaptic terminals
- Both receptors co-localize in GABA-ergic neurons
- Both systems share pharmacologic profiles
- Sedation, antinociception, hypotension, hypothermia, decreased intestinal motility, drug-reward reinforcement
- Naloxone may have effects on the cannabinoid system in several animal models



Indications for cannabis use across included reviews



OPIOID EPIDEMIC

Cannabis and Opioid Relationship

- There is **substantial** evidence that cannabis is an effective treatment for chronic pain in adults (National Academies of Science; 2017)
 - <https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state>
 - Nabiximols, synthetic cannabinoids
 - **NOT** dispensary cannabis/medical cannabis

Cannabis and Opioid Relationship

- Medical cannabis laws are associated with significantly **lower** state-level opioid overdose mortality rates (Bachhuber, JAMA, 2014)
 - <https://pubmed.ncbi.nlm.nih.gov/25154332/>
- Medical cannabis laws are associated with significant **reductions in opioid prescribing** in the Medicare Part D population (Bradford, JAMA, 2018)
 - <https://pubmed.ncbi.nlm.nih.gov/29610897/>

Cannabis and Opioid Relationship

- No evidence that cannabis use reduced pain severity or interference or exerted an opioid-sparing effect (Campbell, Lancet, 2018)
 - <https://pubmed.ncbi.nlm.nih.gov/29976328/>
- States passing a medical cannabis law experienced a 22.7% increase in overdose deaths (Shover, Humphries; Stanford, 2019)
 - <https://www.pnas.org/content/116/26/12624>

Cannabis and Opioid Relationship

- **Data do not strongly support** the use of cannabinoids for **chronic pain** nor do prospective studies demonstrate significant cannabinoid-mediated **opioid-sparing effects** (Babalonis, 2019)
 - <https://www.sciencedirect.com/science/article/pii/S0924977X20300651?via%3Dihub>
- Medical marijuana law enactment was **not associated** with a **reduction** in individual-level non-medical **prescription opioid use**, contradicting the hypothesis that people would substitute marijuana for prescription opioids (Segura, JAMA, 2019)
 - https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2738028?utm_campaign=articlePDF&utm_medium=articlePDFlink&utm_source=articlePDF&utm_content=jamanetw%20orkopen.2019.7216

Cannabis and Opioid Relationship

- No overall protective relationship between state MCLs and opioid overdose (Kim, January 2022)
- This is an additional source of information countering claims of a protective effect of MCLs on opioid overdoses
 - https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2738028?utm_campaign=articlePDF&utm_medium=articlePDFlink&utm_source=articlePDF&utm_content=jamanetworkopen.2019.7216

Cannabis and Opioid Relationship

- March 2022
- Effect of Medical Marijuana Card Ownership on Pain
- Acquisition of a medical marijuana card led to a higher incidence and severity of CUD; resulted in no significant improvement in pain
- <https://pubmed.ncbi.nlm.nih.gov/35302633/>

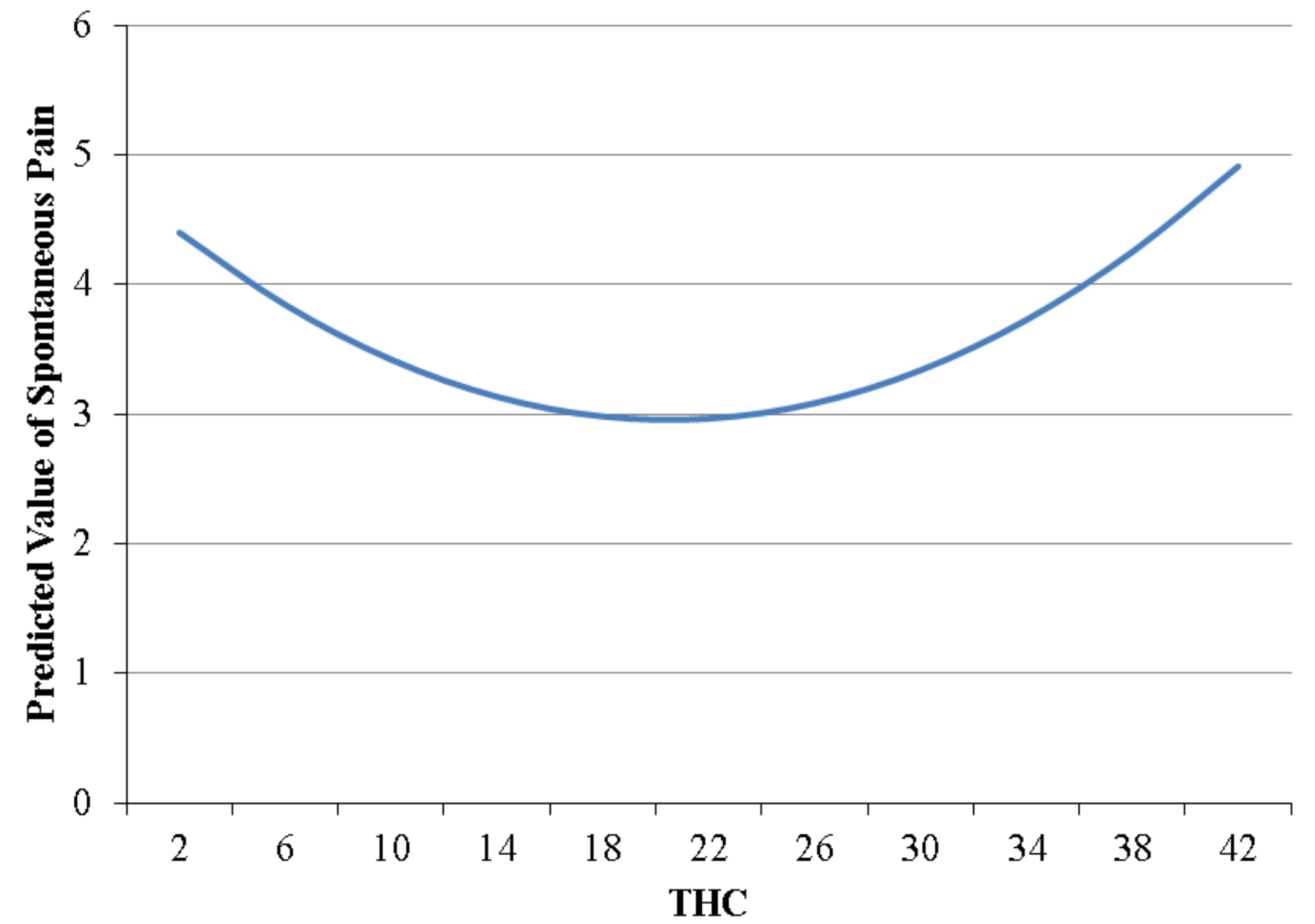
Cannabis and Opioid Relationship

- June 2022
- Primarily neuropathic and arthritic pain
- Oral, **synthetic** cannabis products with high THC-to-CBD ratios and sublingual, **extracted** cannabis products with **comparable** THC-to-CBD ratios **MAY** be associated with short-term improvements in chronic pain and increased risk for dizziness and sedation
- Several limitations, need for more study

THC Plasma Levels and Pain Relief

Therapeutic window of pain relief
between 16-31 ng/ml

- Hyperalgesia
- Note 5ng/ml considered impaired driving although per se limits difficult to determine



Opioid and
Cannabinoid

Receptors

Friends with
Benefits?



Cannabis and Opioid Relationship

- The **number one risk factor** for **adolescent** opioid misuse is having **EVER** use marijuana (lifetime use; YRBS, 2020)
 - https://www.cdc.gov/mmwr/volumes/69/su/su6901a5.htm?s_cid=su6901a5_w
- After 3 years of first trying marijuana vs. opioids, marijuana has a much higher percentage of addiction in **adolescents** (NIH; JAMA Pediatrics, 2020)
 - <https://www.nih.gov/news-events/news-releases/younger-age-first-cannabis-use-or-prescription-drug-misuse-associated-faster-development-substance-use-disorders>
- The **predominant predictor** of **adult** opioid misuse is having used marijuana before the age of 18 (Wadekar)
 - <https://www.sciencedirect.com/science/article/abs/pii/S0376871620300041>

Cannabis and Opioid Relationship

- Cannabis use **increases** the risk of developing opioid use disorder (Olfson)
- <https://pubmed.ncbi.nlm.nih.gov/28946762/>
- Drivers testing positive for marijuana were **28% more likely** to test positive for prescription opioids (FARS, 2017)
- Drivers testing positive for marijuana were **twice as likely** to test positive for prescription opioids (NRS, 2017)
- <https://pubmed.ncbi.nlm.nih.gov/32066484/>

Cannabis and Opioid Relationship

- February 2022
- N: 102,460
- People who use cannabis are disproportionately **more likely** to initiate opioid use and engage in **problematic patterns of use** than people who do not use cannabis
- Need more study

Adolescent Cannabis Use and Opioids

- March 29, 2021; JAMA Pediatrics
- “Within a year of first trying marijuana, 10.7% of adolescents (12-17 yo) had become addicted to it....within three years of first trying the drug, 20% of adolescents became addicted to it.”
- Compared to opioids (11.2%, 10.6%)
- At 3 years of first trying marijuana vs. opioids (12-17 yo), marijuana has a higher percentage of addiction

| STUDY SUBJECTS (FIRST TIME USERS) | ADDICTION RATE AFTER 1 YEAR | ADDICTION RATE AFTER 3 YEARS |
|--------------------------------------|--------------------------------|---------------------------------|
| Cannabis (age 12-17) | 10.7% | 20.1% |
| Cannabis (18-25) | 6.4% | 10.9% |
| Opioid (12-17) | 11.2% | 10.6% |
| Opioid (18-25) | 6.9% | 7.3% |
| Cocaine (18-25) | 5.6% | 6.4% |
| Heroin (18-25) | 30.9% | 42.5% |

Cannabis and Opioid Relationship

- 75,949 adults aged ≥ 50 who participated in the year 2002–2014 (NSDUH)
- **Past-year marijuana use** was significantly associated with an increase in odds of reporting **opioid dependence**, and past-year **non-medical use opioids** (Ramadan, 2020)
- <https://www.tandfonline.com/doi/full/10.1080/10550887.2020.1816117>

Cannabis and Opioid Relationship

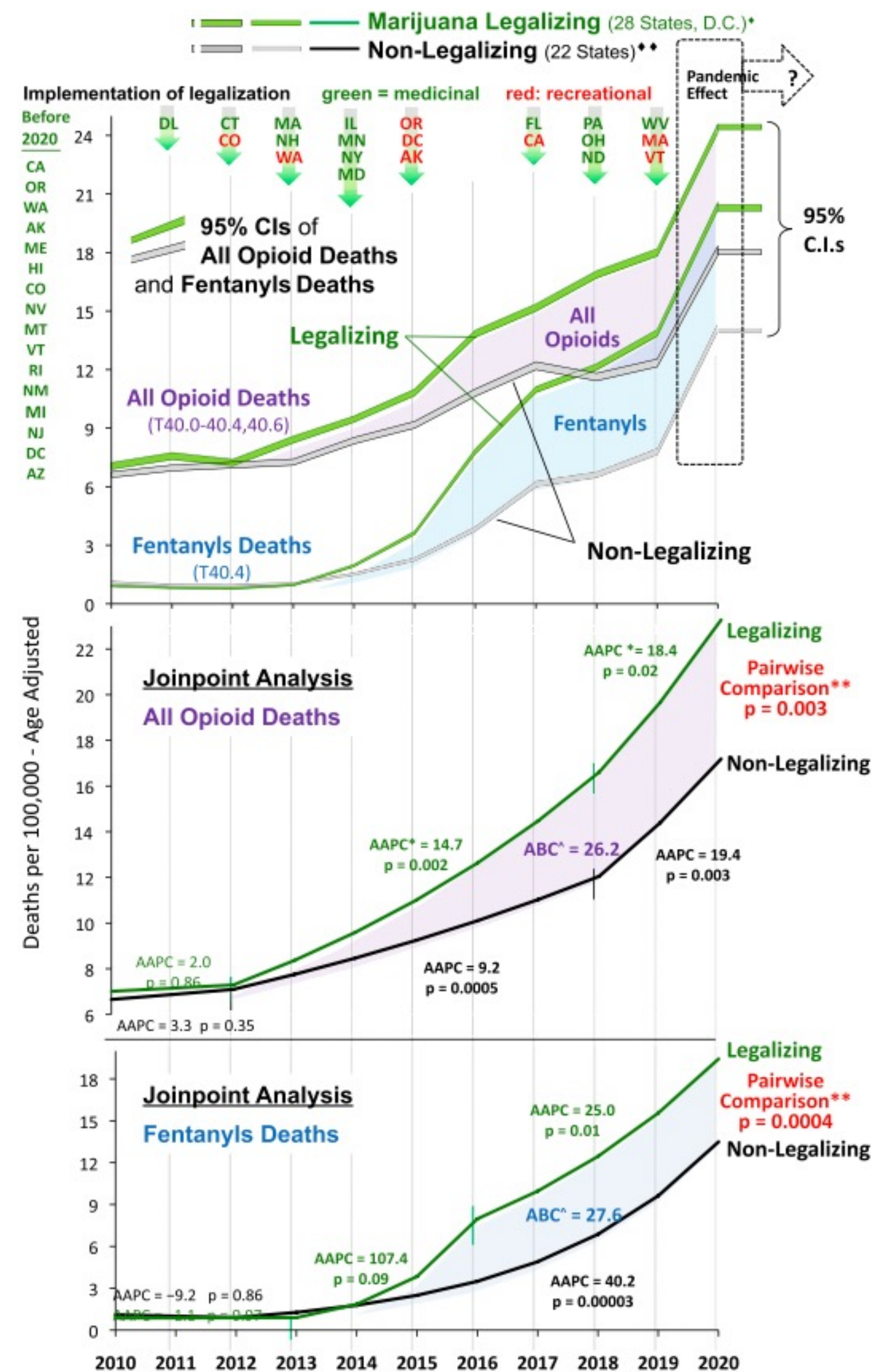
- 2020, October, Turna; Comprehensive Psychiatry; Of all medical users, only **23.4%** reported authorization from a **health professional**
- Medical users modally reported **daily use**
- Compared to recreational users, medical users reported **more problematic cannabis use** in addition to greater psychiatric symptomatology (anxiety, depression and trauma)
- A large majority of **medical users also reported using recreationally (80.6%)**, while exclusive medical use was less common (**19.3%**)

Comprehensive Psychiatry 102 (2020)

<https://reader.elsevier.com/reader/sd/pii/S0010440X20300304?token=ADD81539294C448801520F642E22CC784FE39F6711FABD64204D0616210D1F9C3AF71188EF533AAF47676F8EE3ACDC0D>

Cannabis and Opioid Relationship

- April 22, 2022, (Bleyer, Barnes, Finn)
- One reason is to expect marijuana to help reduce opioid dependence and mortality.
- Opioid deaths have increased more where marijuana was legalized
- This correlation is highly statistically significant for all opioids and fentanyl subgroup



Cancer Pain

- May 2022
- Medical cannabis treatment is generally safe for oncology patients and can potentially reduce the burden of associated symptoms with no serious MC-related adverse effects
- Limitations:
 - Pain was not the only symptom evaluated
 - Product variability and inconsistent

Cancer Pain

- Sativex **failed** to show superiority over placebo in two Phase III trials
- Sativex **did not demonstrate superiority** to placebo in reducing self-reported pain NRS scores in advanced cancer patients with **chronic pain** unalleviated by optimized opioid therapy

IASP/ANZCA

- 2021, International Association for the Study of Pain
 - Due to the lack of high-quality clinical evidence, IASP does not currently endorse general use of cannabis and cannabinoids for pain relief.
- 2021, Australian and New Zealand College of Anaesthetists, Faculty of Pain Medicine
 - The evidence available is either unsupportive of using cannabinoid products in chronic non-cancer pain (CNCP), or is of such low quality that no valid scientific conclusion can be drawn

https://journals.lww.com/pain/toc/2021/07001?mkt_tok=NjgxLUZIRS00MjkAAAF-ZOn80Q54bTKbENgZ3CikwcGIDuzvbXB0sth7I0yLASDAqkmUhNSUWJMXyEsUCpb72qELLRWvatQm0HzsEL00wg7Oibe363pyu8vEngW4QtH78YSqvg
<https://www.choosingwisely.org.au/recommendations/fpm6>

Australian Pain Society



- Relies heavily on the International Association for the Study of Pain as well as the Australian and New Zealand College of Anesthetists, Faculty of Pain Medicine

<https://www.apsoc.org.au/position-papers>

New Zealand Pain Society



- Relies heavily on the International Association for the Study of Pain as well as the Australian and New Zealand College of Anesthetists, Faculty of Pain Medicine

<https://www.apsoc.org.au/position-papers>

British Pain Society

2018

- Meta-analyses of clinical studies on cannabinoids for the management of pain conclude that there is **no positive evidence** to support routine use in pain management
- These include neuropathic pain, chronic non-malignant pain and cancer pain
- The quality of some studies is **not of a high standard** and supports the need of well-designed robust clinical trials
- More reliable evidence is warranted following robust clinical evaluation

European Pain Federation 2018

- Registered medicinal cannabis extracts with **defined and standardized** THC and THC/CBD content should be classified as ‘cannabis-derived’ or ‘cannabis-based’ medicines.
- There are **differences** in the approval and availability of medical cannabis and cannabis-based medicines
- There is **insufficient evidence** as to whether medical cannabis and cannabis-based medicines differ in their efficacy, tolerability and safety.
- **Do not prescribe** cannabis-based medicines to patients taking high doses of **opioids or benzodiazepines**.
- **Do not prescribe** cannabis flowers with a **high (>12.5%) THC content**

<https://onlinelibrary.wiley.com/doi/pdfdirect/10.1002/ejp.1297>

National Institute on Health Care and Excellence

United Kingdom, Nov 2019

- Do not offer the following to manage chronic pain in adults:
 - Nabilone
 - Dronabinol
 - THC (delta-9-tetrahydrocannabinol)
 - a combination of cannabidiol with THC
- Do not offer CBD to manage chronic pain in adults unless as part of a clinical trial.

Colorado Medical Society

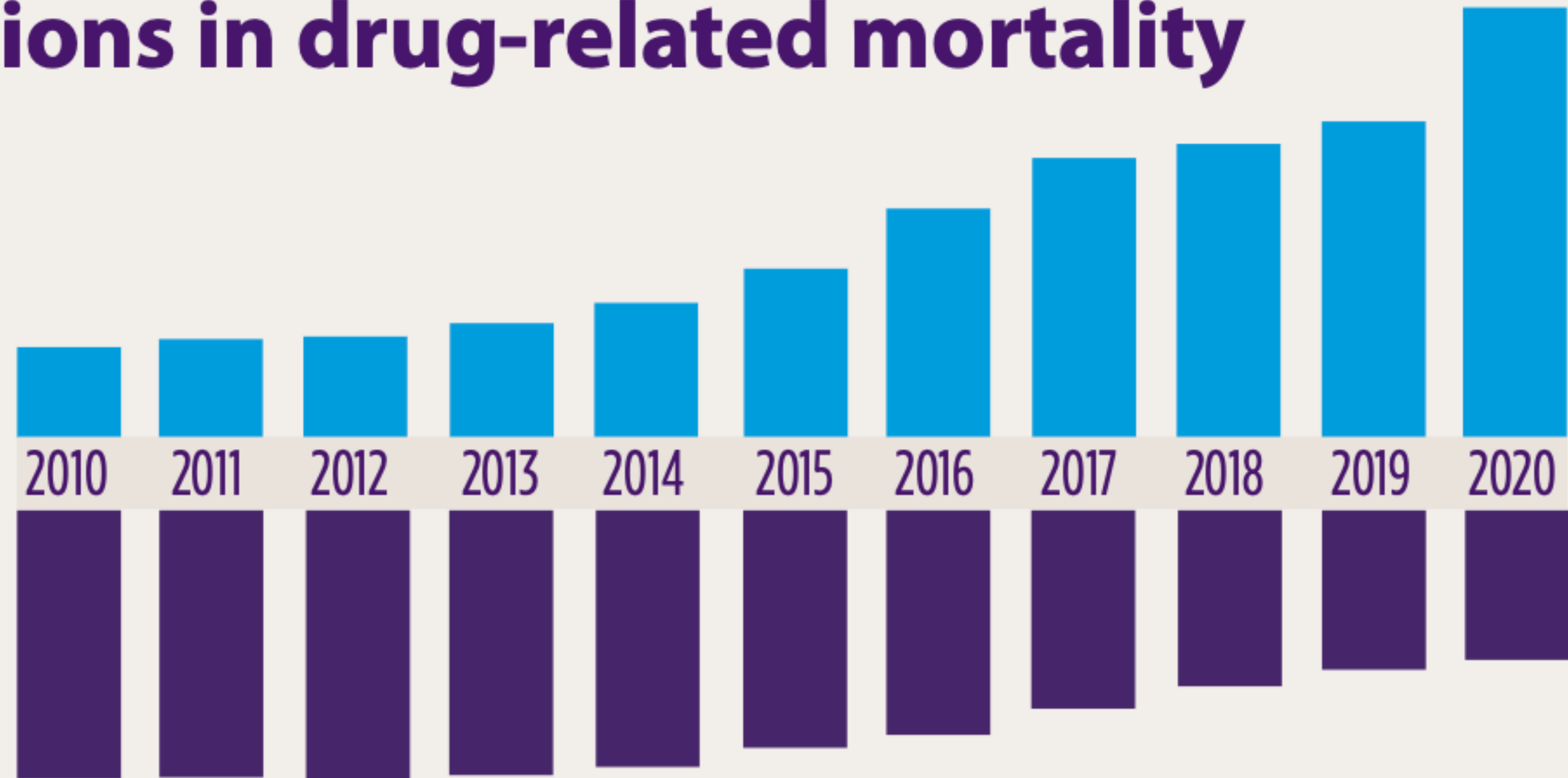
- Opposes inhalation of cannabinoids due to negative health effects
- Opposes self-diagnosing and treating medical conditions
- Recommends any consideration of use for “medical” purposes be under the supervision of providers practicing “within their scope of training”
- Recommends specific time frames of care
- Bonafide doctor-patient relationships and maintaining medical records
- Recommends 15% potency limit

<http://www.cms.org/about/policies/#145-drug-abuse>

Reductions in opioid prescribing have not led to reductions in drug-related mortality

Overdose deaths:
94,134*

Opioid prescriptions:
143,390,951¹
(44.4% decrease
since 2011)



*Provisional data for the 12-month period Jan. 2020–Jan. 2021
<https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>

Drug overdose deaths in the U.S.

Annual deaths ending in November of each year below

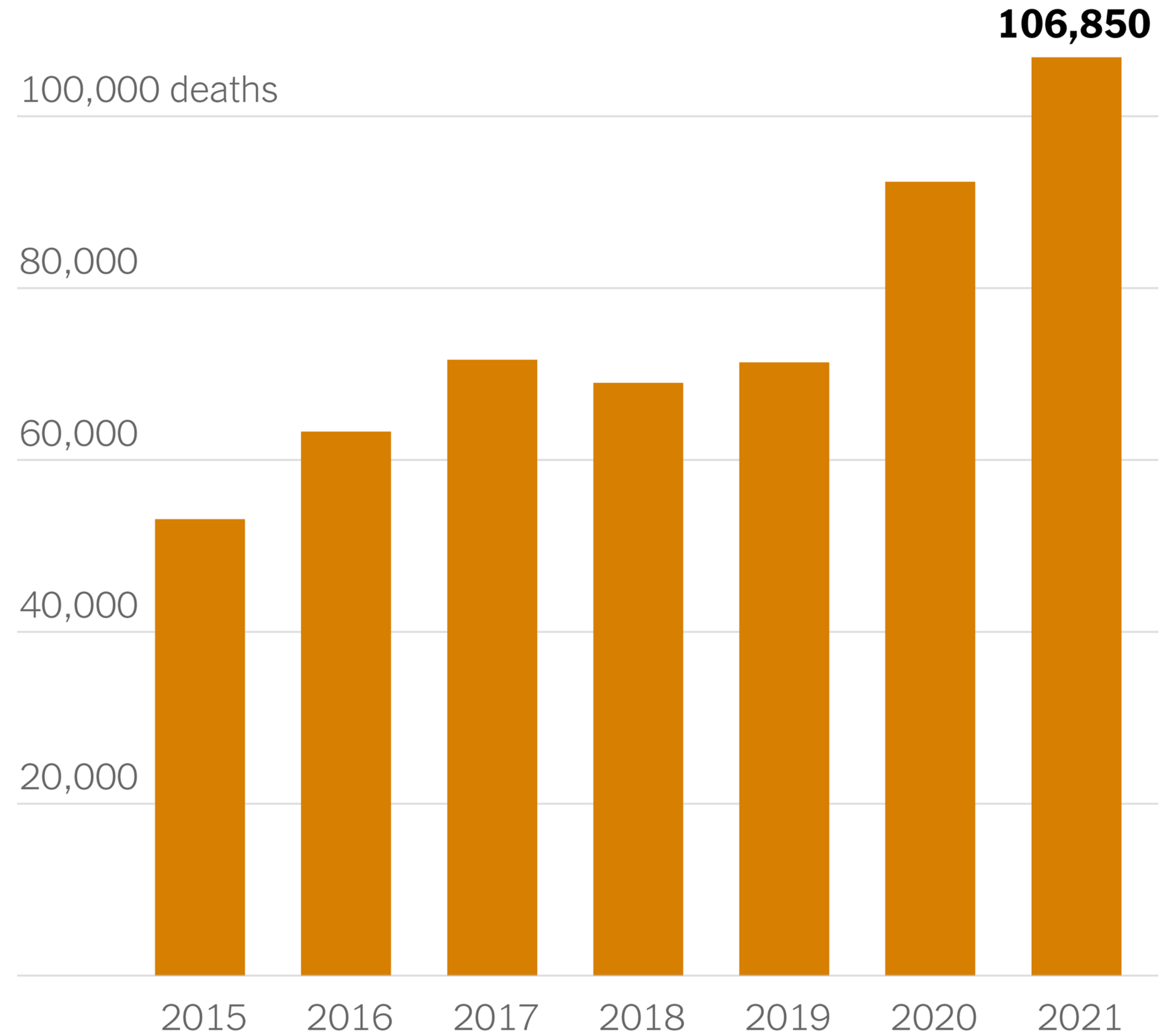
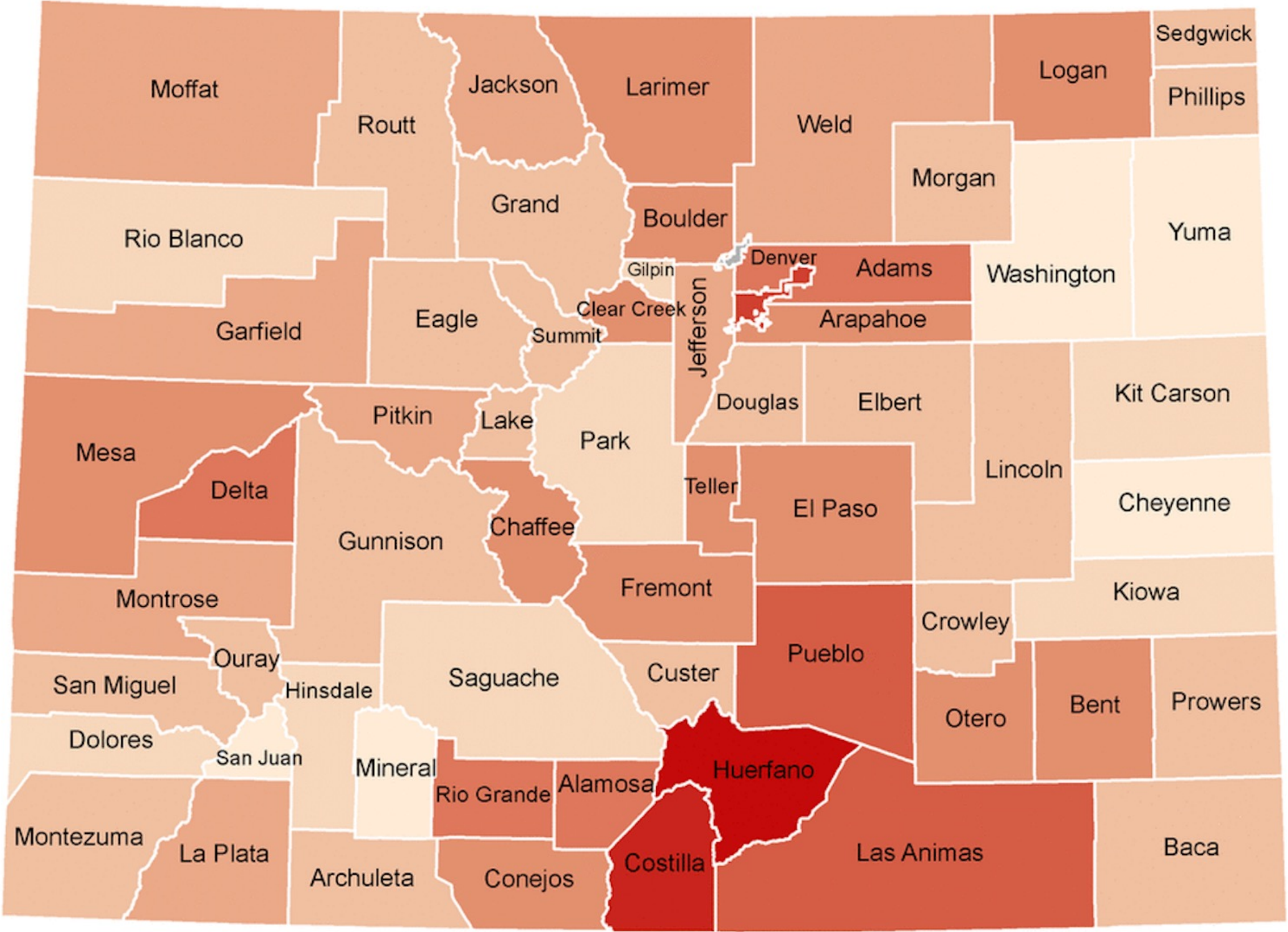


Chart shows provisional figures. | Source: Centers for Disease Control and Prevention

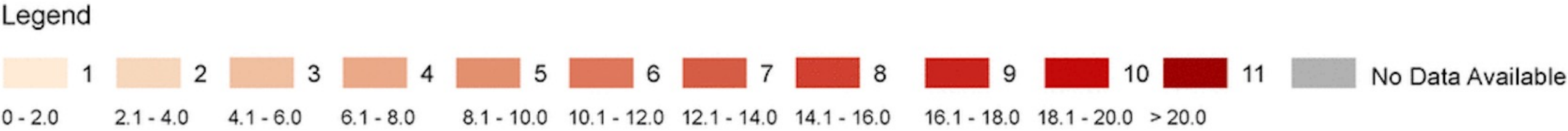
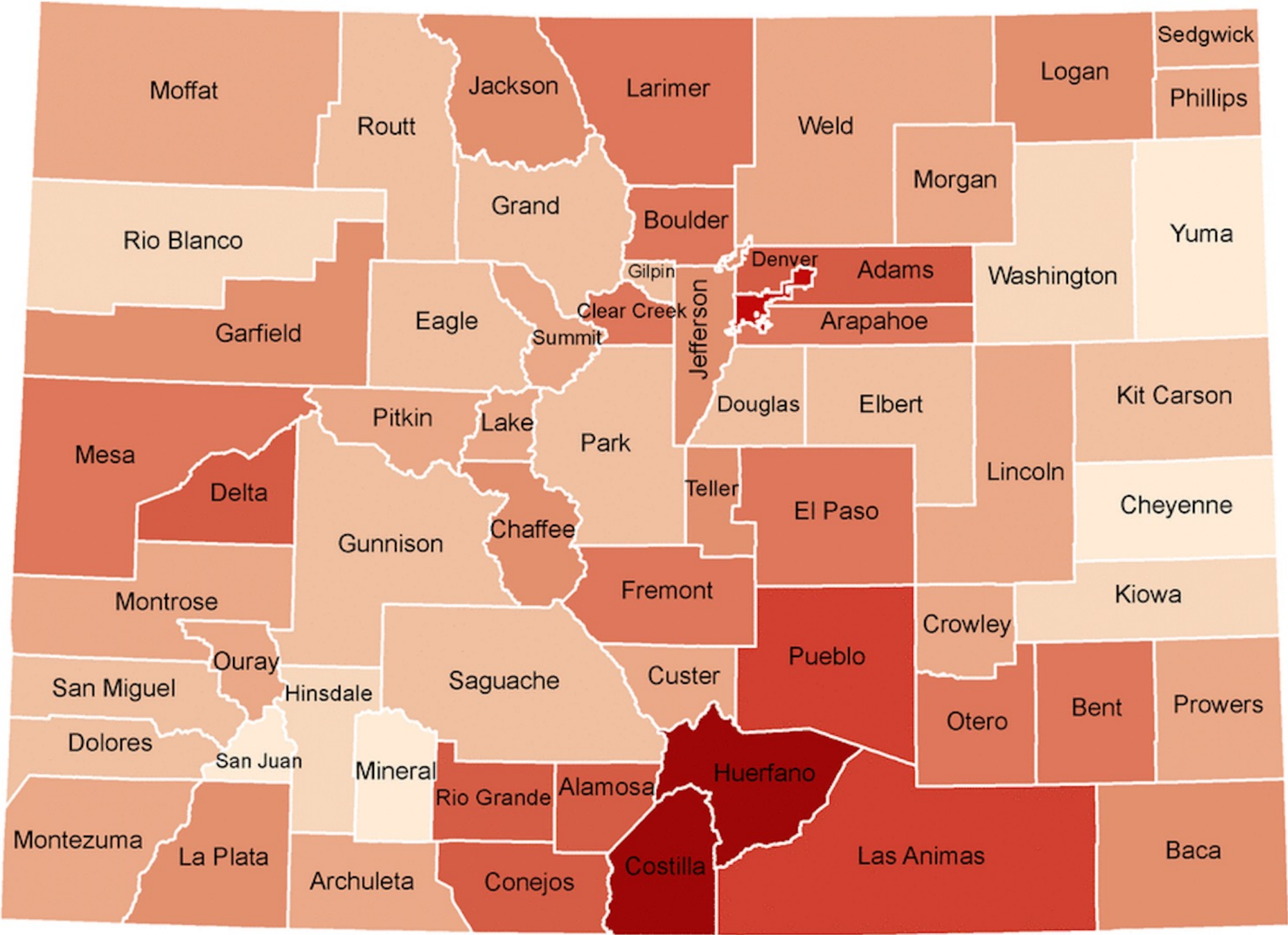
Colorado Health Institute Opioid Overdose Deaths by County 2002-2014

coloradohealthinstitute.org

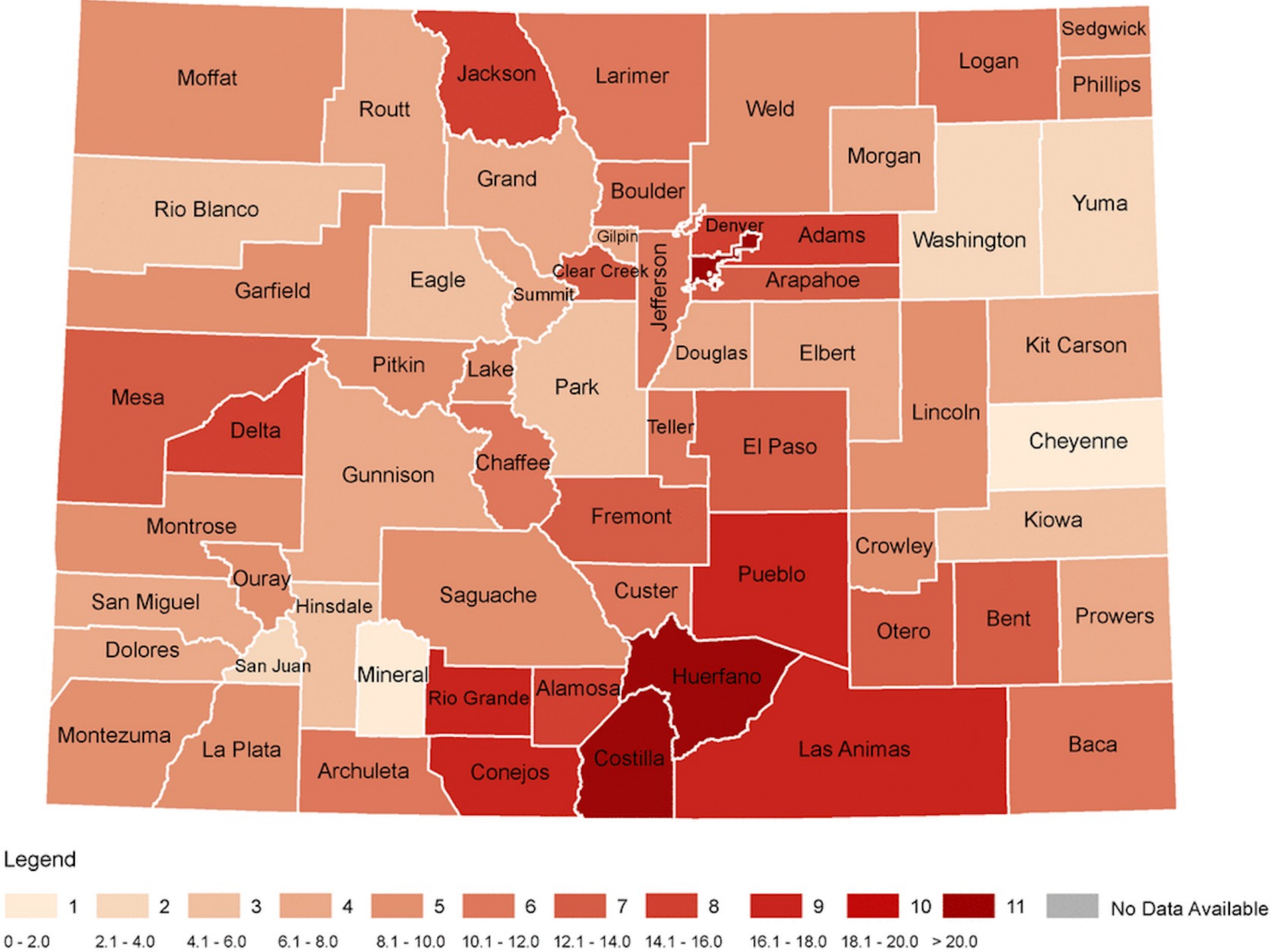
Colorado Drug Overdose Death Rate, 2002



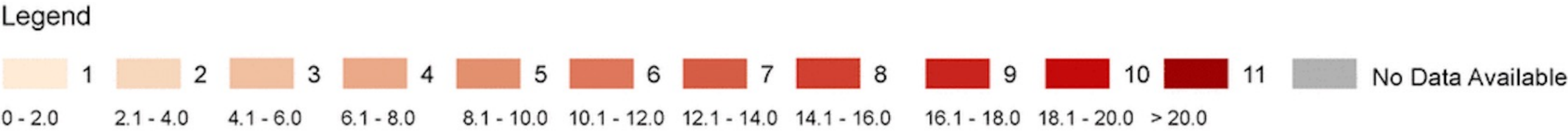
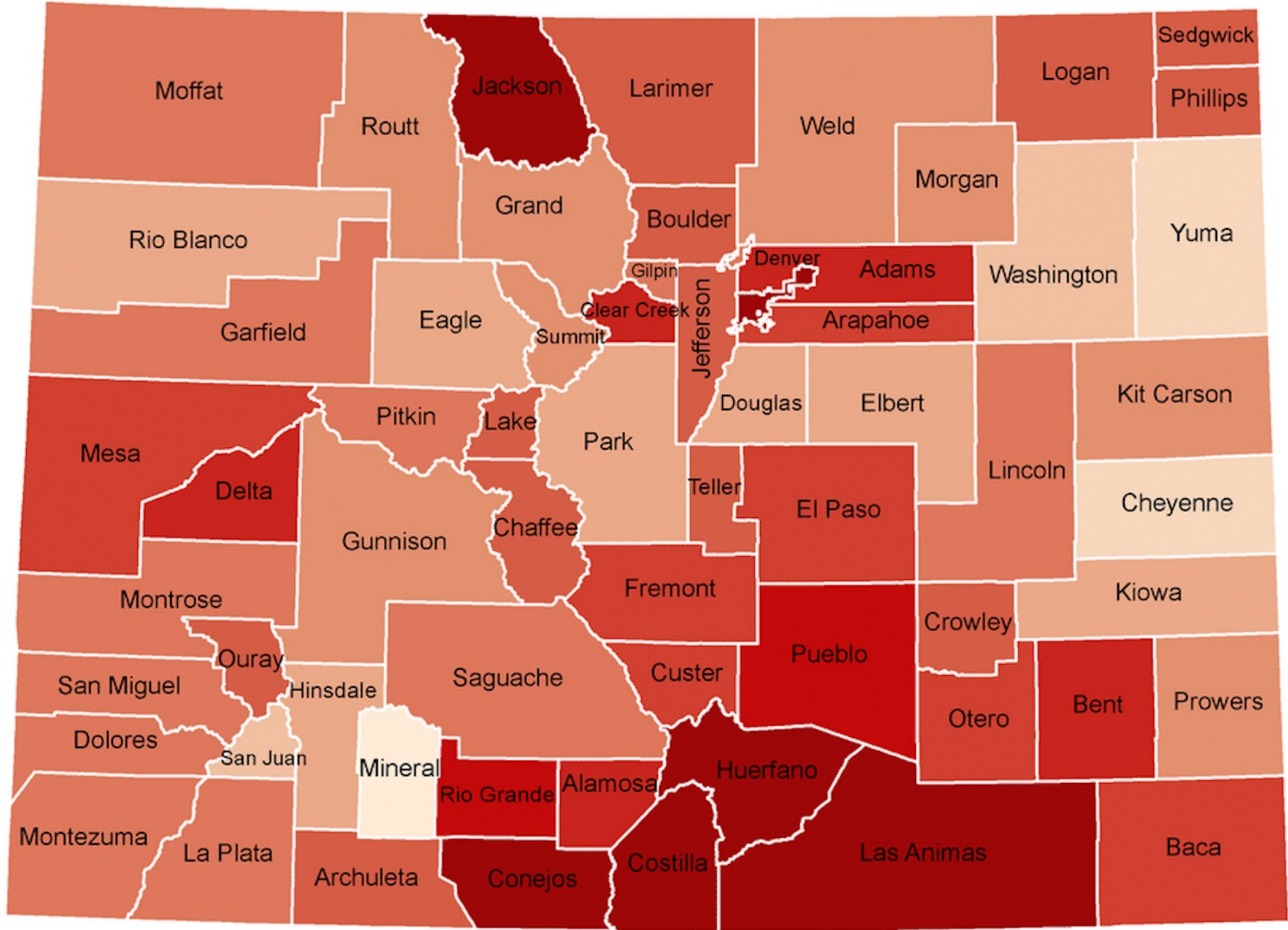
Colorado Drug Overdose Death Rate, 2005



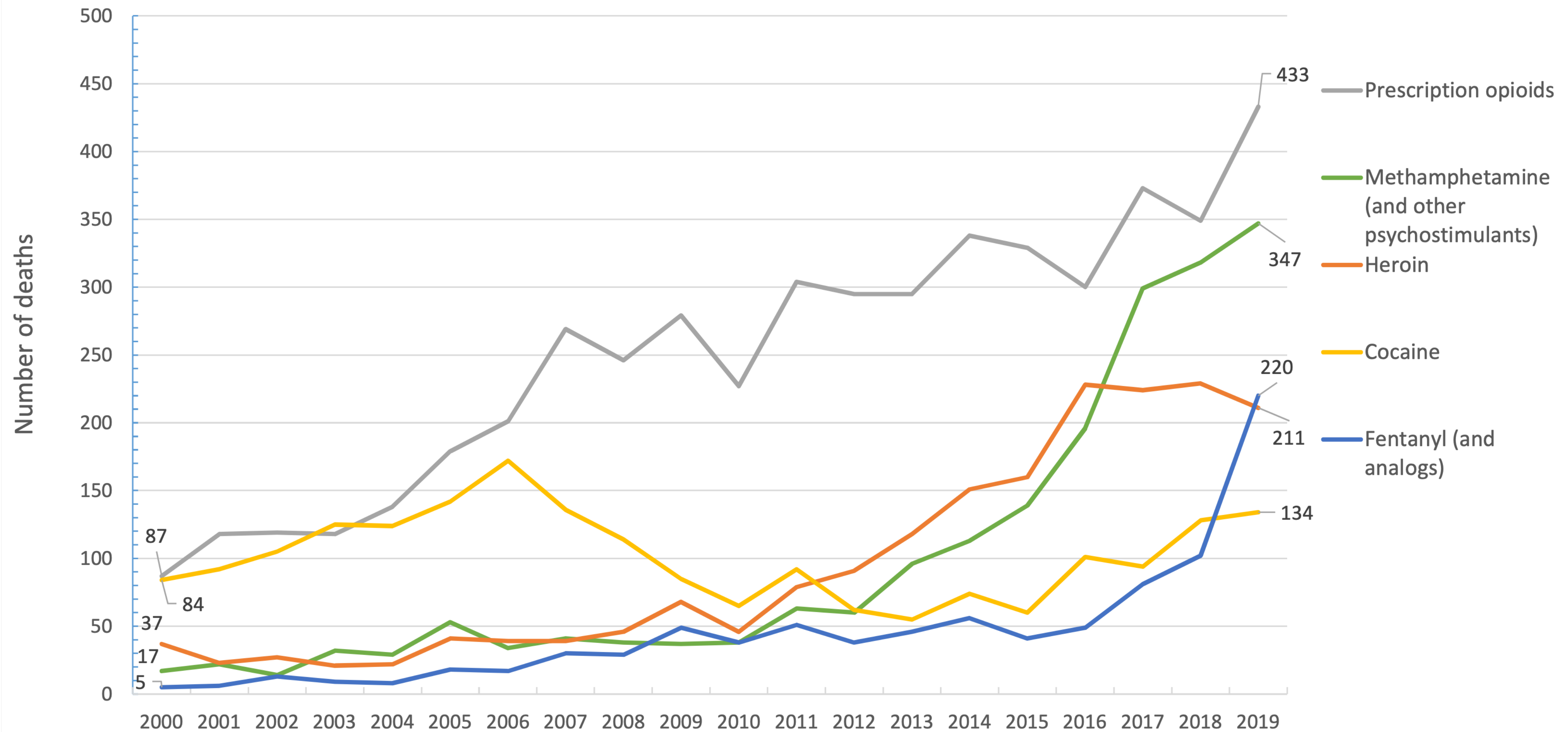
Colorado Drug Overdose Death Rate, 2008



Colorado Drug Overdose Death Rate, 2011



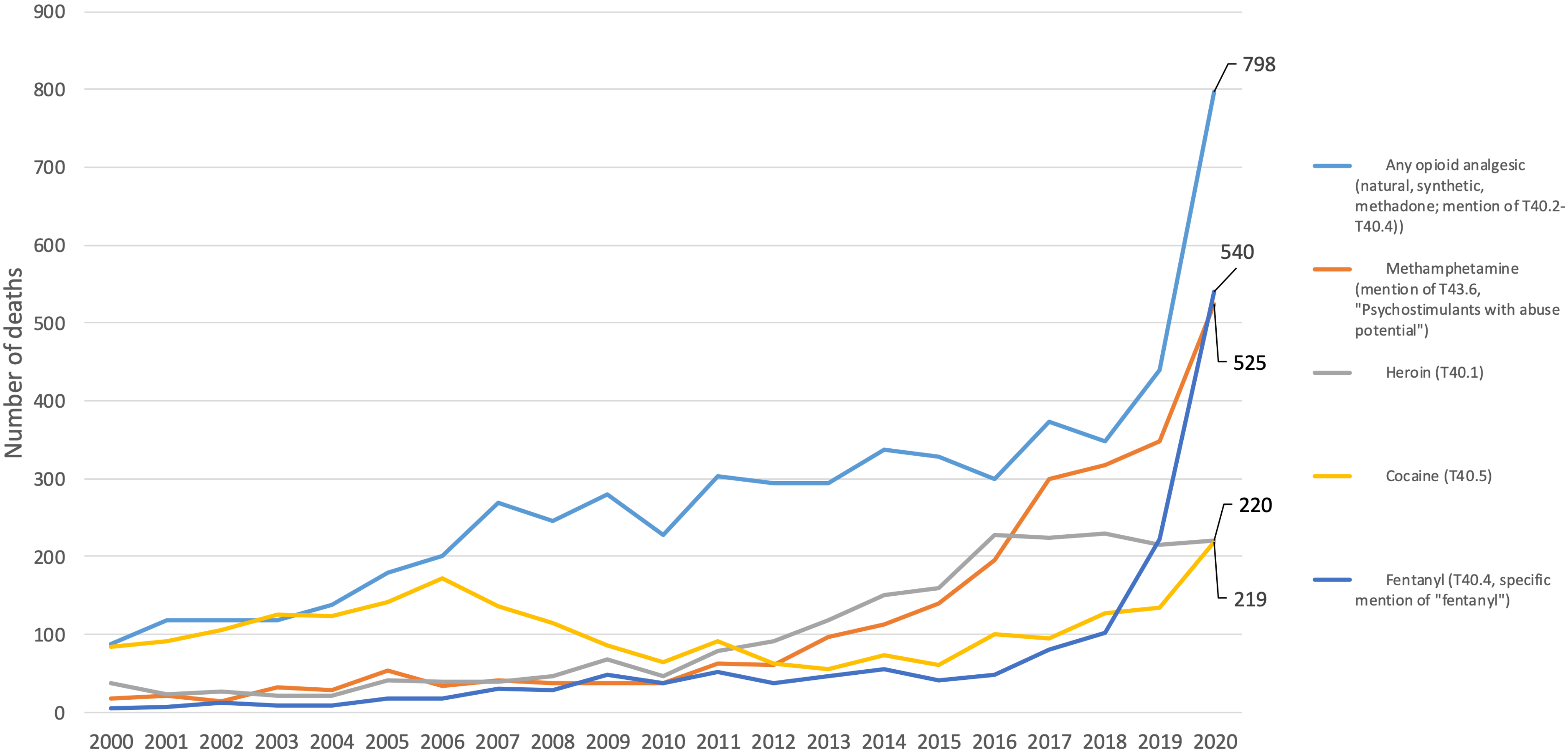
Number of drug overdose deaths by substances mentioned: Colorado residents, 2000-2019



Source: Vital Statistics Program, Colorado Department of Public Health and Environment

2019 data shows a **24% increase** (433 total) in prescription opioid overdose deaths and **115% increase** (220 total) in fentanyl deaths

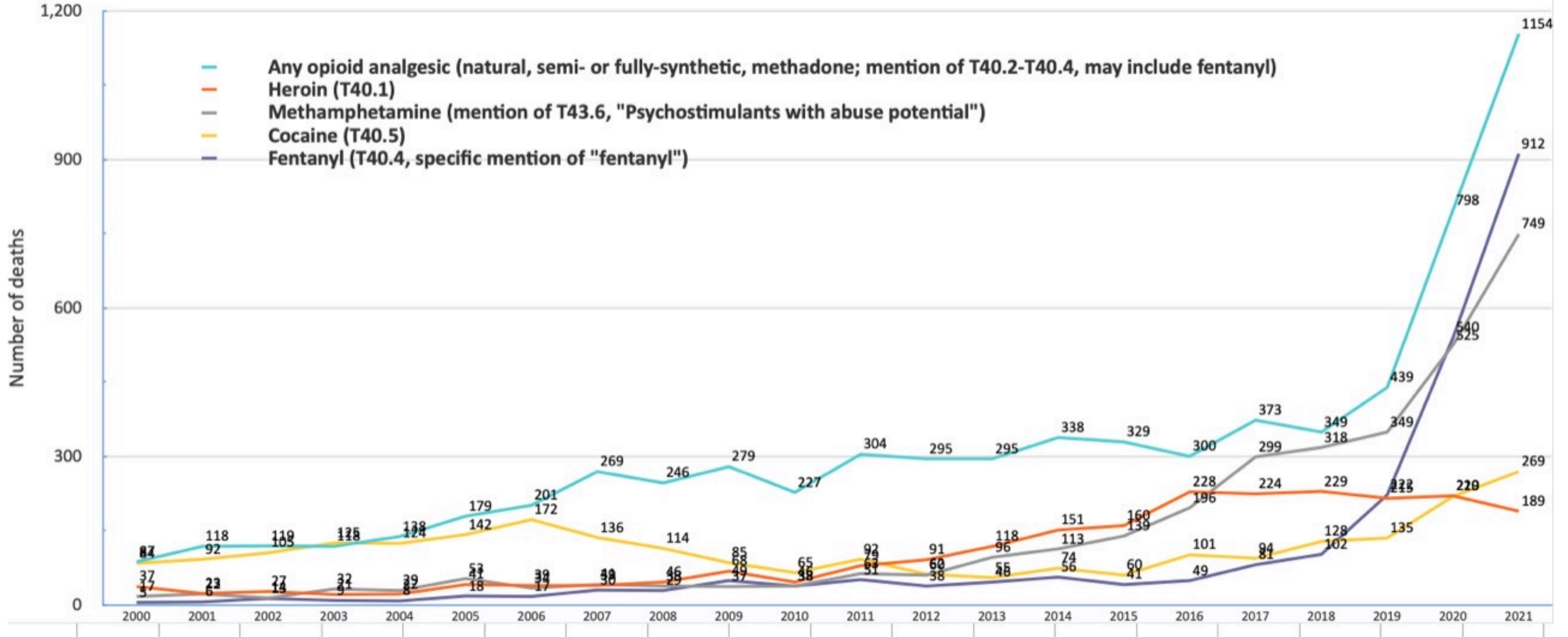
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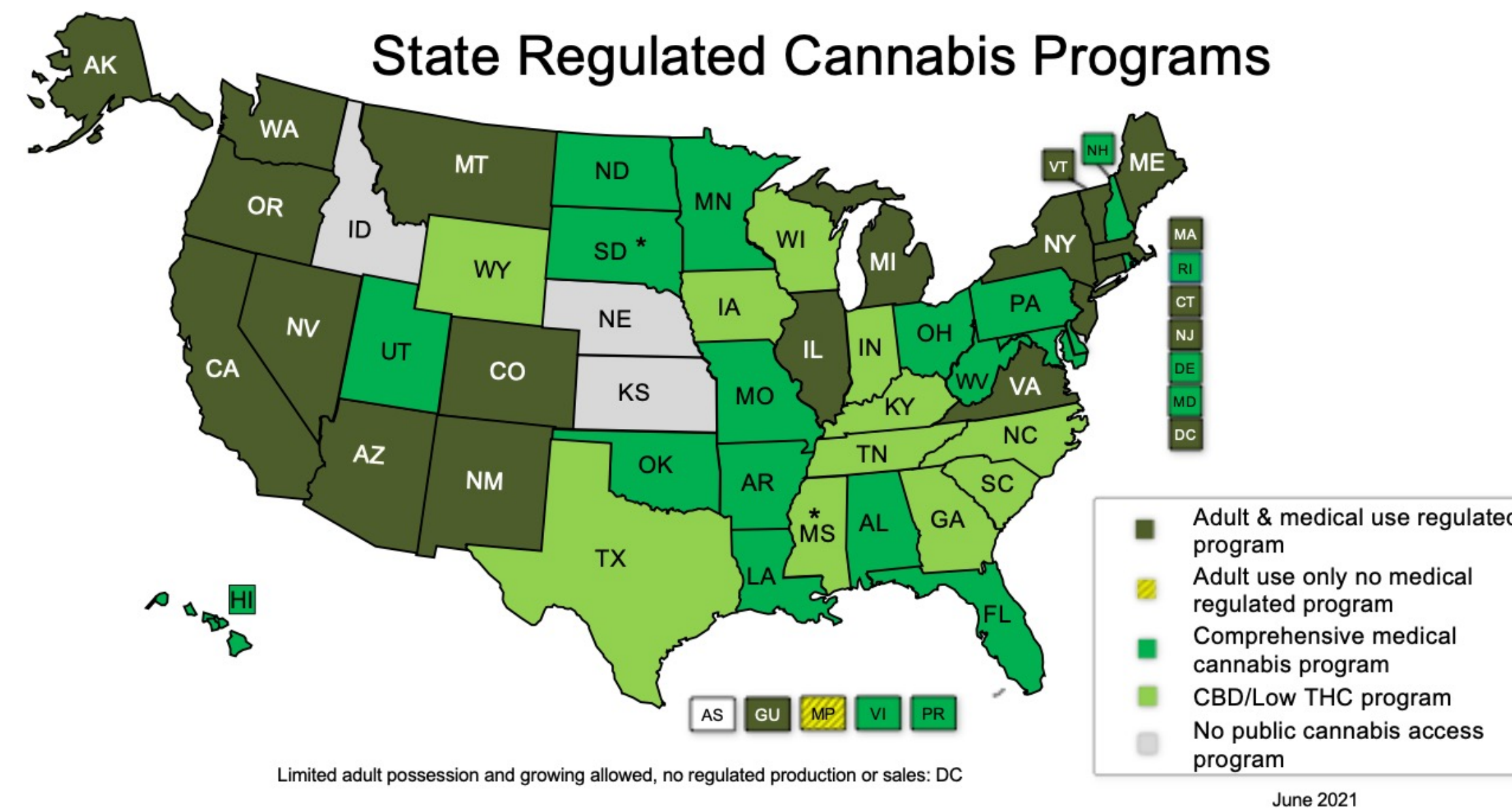
Drug overdose deaths by category of specific drug involvement: 2000-2021

Colorado residents,



More States Legalize Marijuana, 2021

- As of May 18, 2021, 36 states and four territories allow for the medical use of cannabis products.
- <https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx#1>

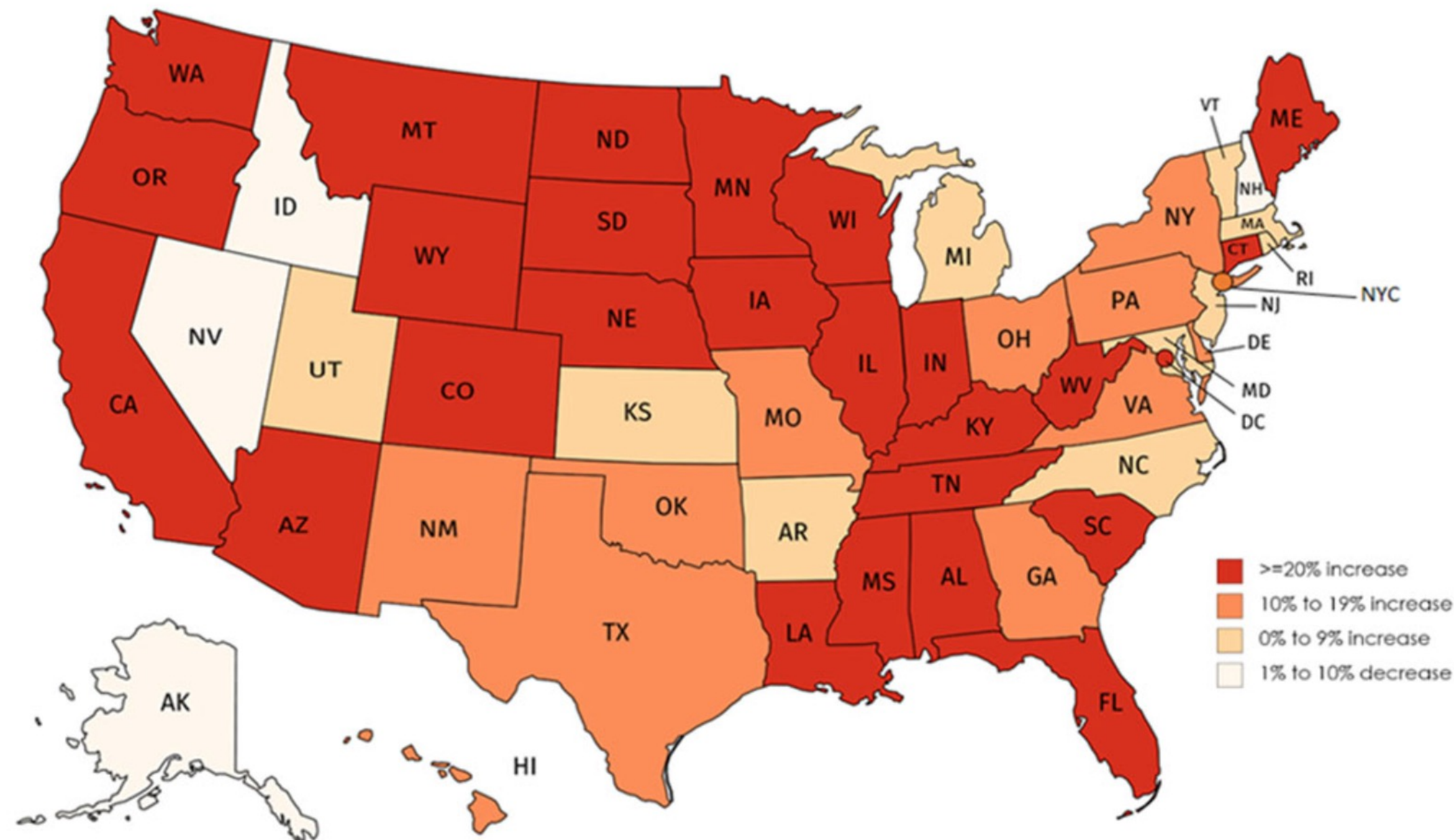


* = 2020 measures in Mississippi for medical use and South Dakota for nonmedical use were overturned in 2021.

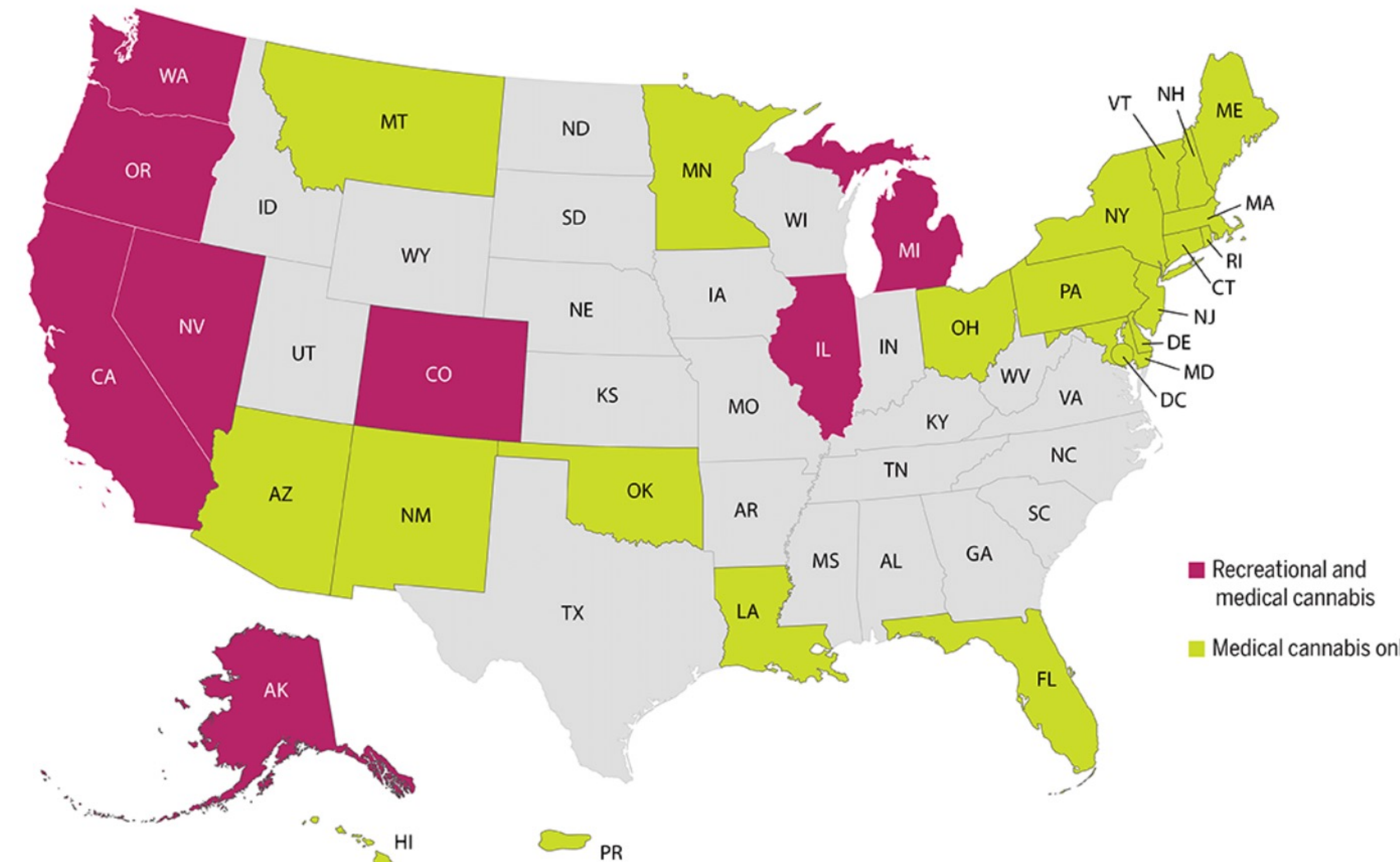


Drug Overdoses and Marijuana is “Essential”

Figure 2: Percentage change in 12-months ending provisional^a data on all fatal drug overdoses^b, 50 states, the District of Columbia, and New York City: Overdose deaths from 12-months ending in June 2019 to 12-months ending in May 2020^c



States allowing marijuana businesses to operate despite lockdown/stay-at-home orders*



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*As of 10 a.m. MT April 2

Distributed via the CDC Health Alert Network
December 17, 2020, 8:00 AM ET

Cannabis and Opioids

- There is **no evidence** supporting the use of **dispensary** cannabis for chronic non-cancer pain
- There is no **package insert** for **dispensary** cannabis
- There is **no evidence** for substituting opioids with **dispensary** cannabis
- Cannabis users are **more likely** to develop opioid use disorder or misuse their opioids and have higher depression and anxiety scores, and other negative psychiatric effects
- States with medical marijuana programs typically have **higher opioid overdose deaths** than non-medical marijuana states
- Any real or perceived benefit **outweighed** by current evidence

Action Plan

- Cannabis is not a medication. Cannabis is a plant
- Support drug-development process for cannabinoids, including evidence-based dosing guidelines of cannabis-based medications
- Support potency cap (15% THC)
- Eliminate home grows: breeding ground for illegal activity
- Track, monitor, and document public health impact (health care utilization, ER, birth defects, etc)
- Monitor and publish environmental impacts

Action Plan

- Mandatory drug testing for all violent crimes (cannabis induced psychosis)
- Monitor adolescent use closely
- Discourage smoking and vaping (EVALI)
- Discourage use during pregnancy and lactation
- Drug testing/toxicology on all suicides, including adolescents
- Monitor marijuana-related driving fatalities

Kenneth Finn *Editor*
Cannabis in Medicine
An Evidence Based Approach

Legalization of marijuana is becoming increasingly prominent in the United States and around the world. While there is some discussion of the relationship between marijuana and overall health, a comprehensive resource that outlines the medical literature for several organ systems, as well as non-medical societal effects, has yet to be seen. While all physicians strive to practice evidence-based medicine, many clinicians aren't aware of the facts surrounding cannabis and are guided by public opinion.

This first of its kind book is a comprehensive compilation of multiple facets of cannabis recommendation, use and effects from a variety of different perspectives. Comprised of chapters dedicated to separate fields of medicine, this evidence-based guide outlines the current data, or lack thereof, as well as the need for further study. The book begins with a general overview of the neurobiology and pharmacology of THC and hemp. It then delves into various medical concerns that plague specific disciplines of medicine such as psychiatry, cardiology, gastrointestinal and neurology, among others. The end of the book focuses on non-medical concerns such as public health and safety, driving impairment and legal implications.

Comprised of case studies and meta-analyses, *Cannabinoids in Medicine: An Evidence-Based Approach* provides clinicians with a concise, evidence-based guide to various health concerns related to the use of marijuana. By addressing non-medical concerns, this book is also a useful resource for professionals working in the public health and legal fields.

Finn *Ed.*



Cannabis in Medicine

Cannabis in Medicine

An Evidence Based Approach

Kenneth Finn
Editor

<https://www.springer.com/us/book/9783030459673>



<https://iasic1.org>