RADARS® SYSTEM 2023

17TH ANNUAL SCIENTIFIC VIRTUAL MEETING

Satisfying the Craving for Novel Psychoactive Post-Market Surveillance

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Professor of Emergency Medicine & Medical Toxicology

&

Scientific Director RMPDS

Wednesday, May 10, 2023

Disclosures

- I serve on the CDPHE Retail Marijuana Public Health Advisory Committee
- I am a co-investigator on FDA: General Online Longitudinal Drug use Survey (GOLDS)
- I am funded through NIDA for development of a cellular assay for synthetic cannabinoids
- RMPDS is funded by a range of pharmaceutical companies and governmental organizations for pharmacovigilance, assessment of adverse events, response to risk mitigation strategies, and research in field of Toxicology

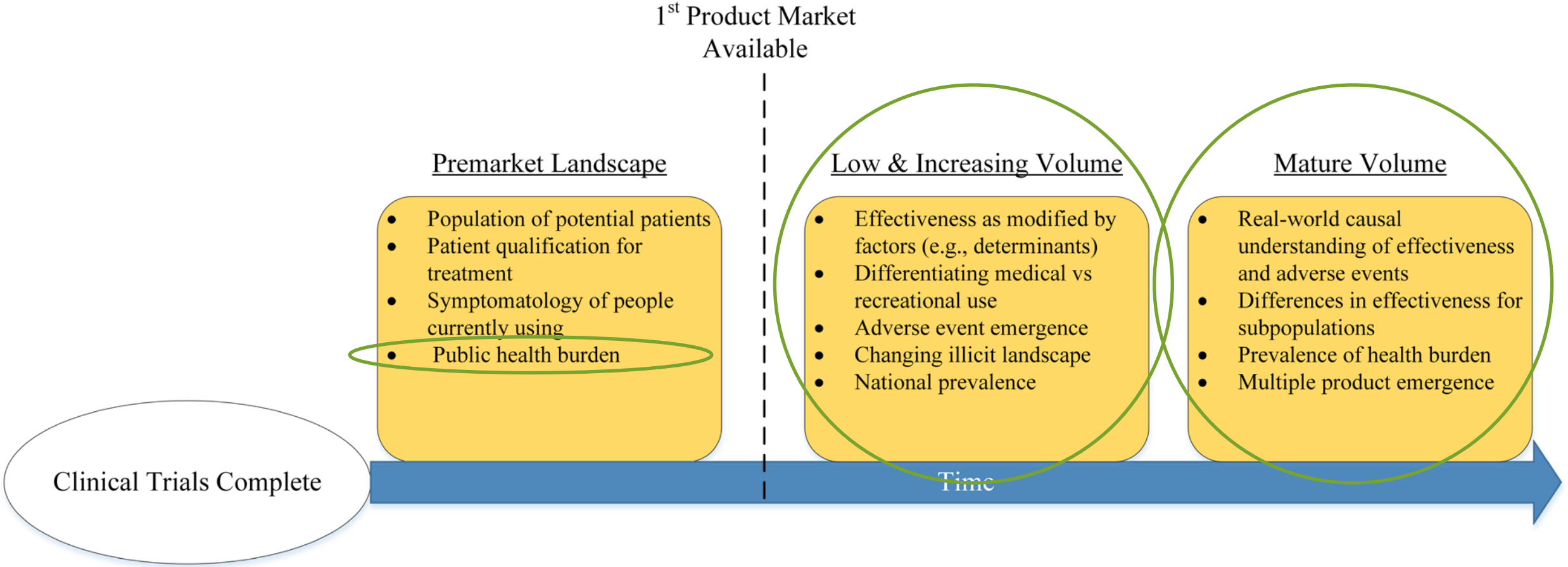
Objectives

- Identify surveillance tools necessary for new drugs with regional use patterns, legal status differences, and rapidly expanding indications.
- Identify gaps in data collection tools.
  - The role of effectiveness in safety
  - Cannabinoid hyperemesis example
- New tools to fill these gaps

21 yo F with hx of numerous bowel surgeries admitted for pain control.

- History of treatment resistant depression and chronic pain.
- Has been decreased from previous opioid therapies by her pain physician.
- Had ketamine infusion of 450 mg over 2 hours weekly x 3 weeks at local treatment center.
- Has severe hallucinations day of and into next morning.
- Uses compounded ketamine nasal 30 mg 3-4 times daily on “good pain days”, 6-8 times daily on “bad pain days”.
- Reports tolerance to ketamine increasing.

Evolving Research Needs as Market Expands



Thanks to Joshua Black for this slide

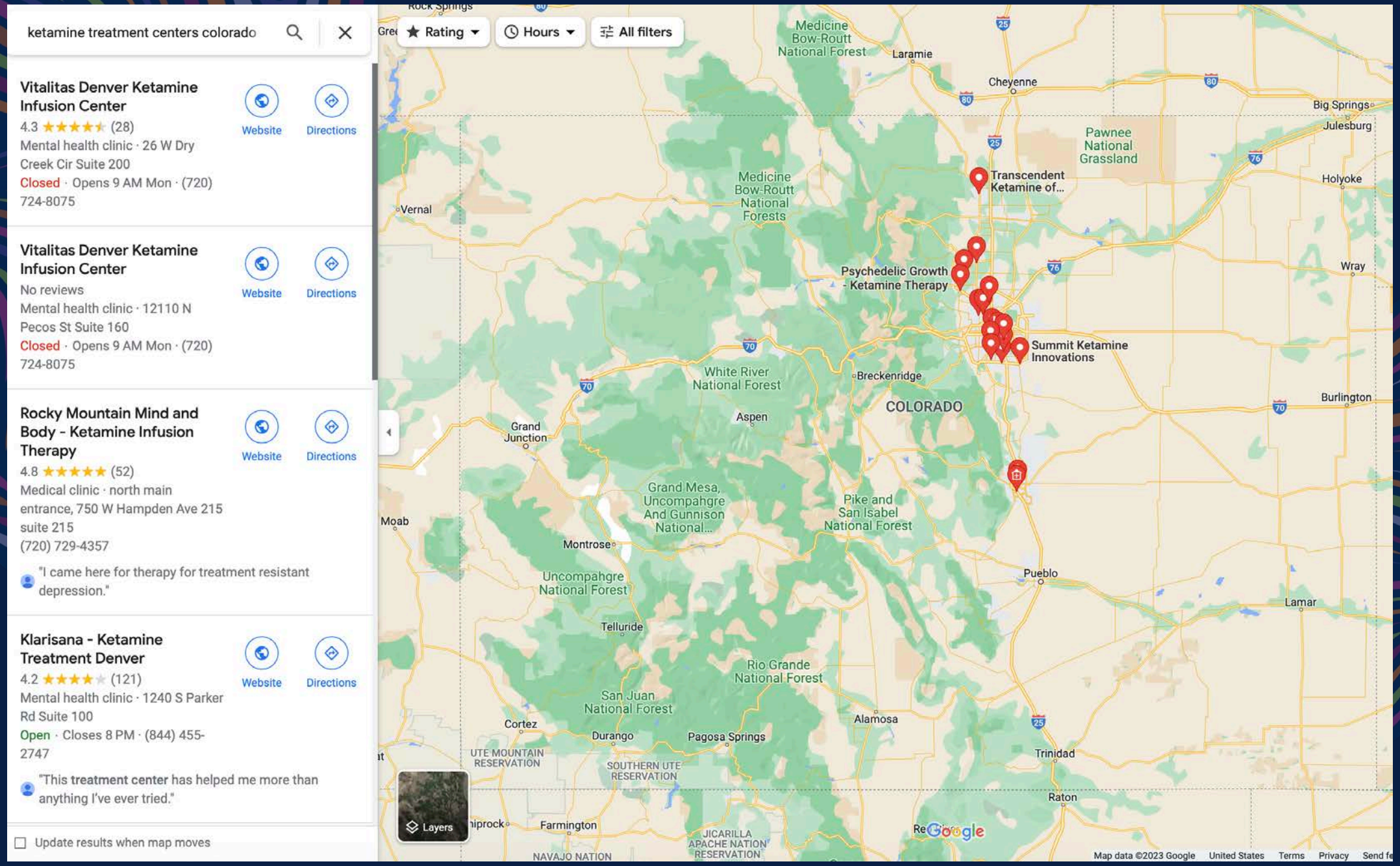
Necessary Surveillance Components for These Drugs

- Small area assessment

Psychedelic use has increased in liberalized states

Study Period	Past Year Use % CO/OR (95% CI)	Past Year Use % All Other States (95% CI)
2019-2020	3.3 (2.7, 3.9)	2.4 (2.3, 2.5)
2021-2022	5.4 (4.5, 6.2)	2.8 (2.7, 3.9)

Data from NMURx Survey


ketamine treatment centers colorado
Rating
Hours
All filters
Vitalitas Denver Ketamine Infusion Center
4.3 (28)
Mental health clinic · 26 W Dry Creek Cir Suite 200
Closed · Opens 9 AM Mon · (720) 724-8075
Website
Directions
Vitalitas Denver Ketamine Infusion Center
No reviews
Mental health clinic · 12110 N Pecos St Suite 160
Closed · Opens 9 AM Mon · (720) 724-8075
Website
Directions
Rocky Mountain Mind and Body - Ketamine Infusion Therapy
4.8 (52)
Medical clinic · north main entrance, 750 W Hampden Ave 215 suite 215
(720) 729-4357
"I came here for therapy for treatment resistant depression."
Website
Directions
Klarisana - Ketamine Treatment Denver
4.2 (121)
Mental health clinic · 1240 S Parker Rd Suite 100
Open · Closes 8 PM · (844) 455-2747
"This treatment center has helped me more than anything I've ever tried."
Website
Directions
Update results when map moves
Transcendent Ketamine of...
Psychedelic Growth - Ketamine Therapy
Summit Ketamine Innovations
Medicine Bow-Routt National Forest
Laramie
Cheyenne
Big Springs
Julesburg
Pawnee National Grassland
Holyoke
Wray
Burlington
Vernal
Medicine Bow-Routt National Forests
White River National Forest
Breckenridge
COLORADO
Aspen
Grand Junction
Grand Mesa, Uncompahgre And Gunnison National...
Pike and San Isabel National Forest
Moab
Montrose
Uncompahgre National Forest
Telluride
Pueblo
Lamar
Rio Grande National Forest
San Juan National Forest
Cortez
Durango
Pagosa Springs
Alamosa
Trinidad
Raton
UTE MOUNTAIN RESERVATION
SOUTHERN UTE RESERVATION
Farmington
JICARILLA APACHE NATION RESERVATION
NAVAJO NATION
Layers
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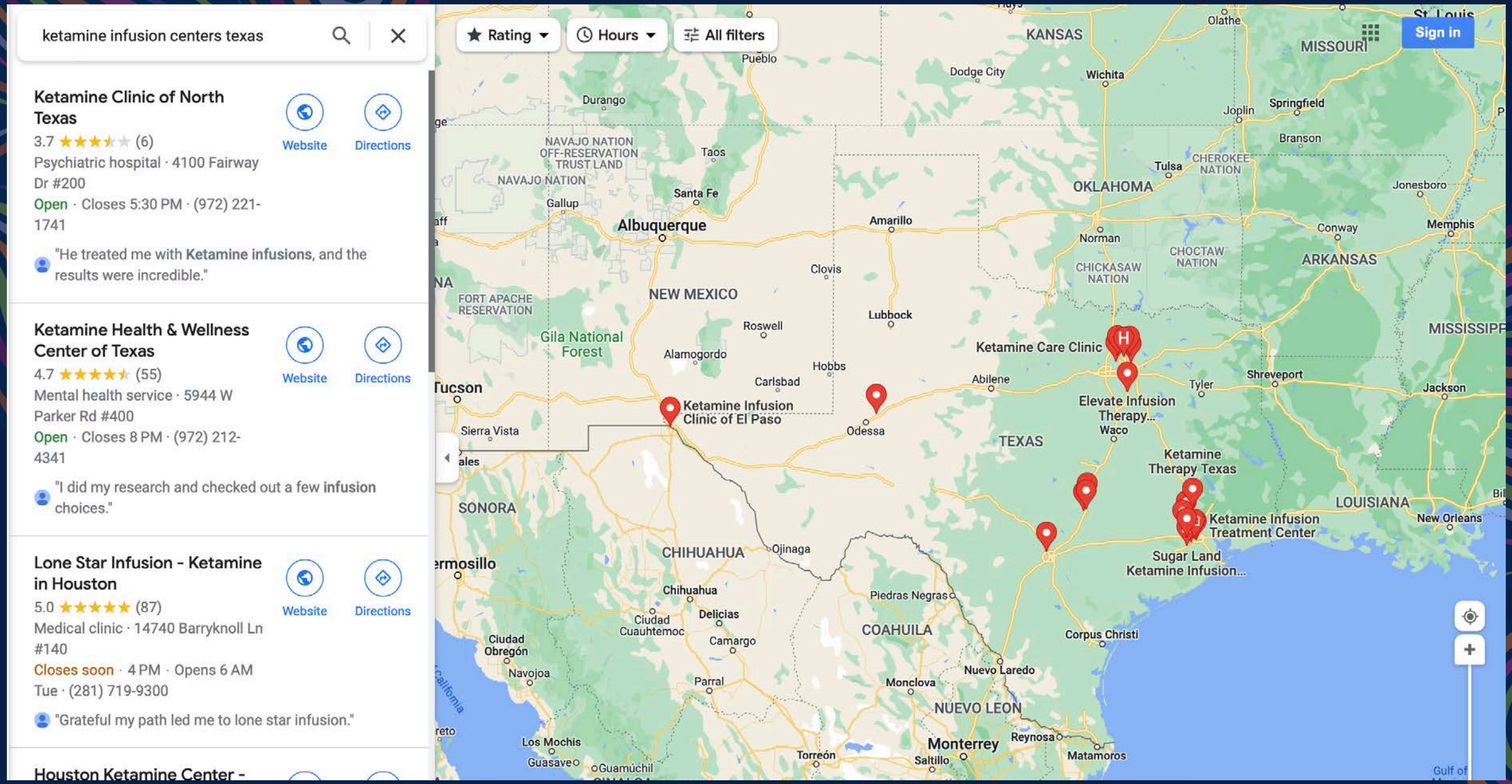
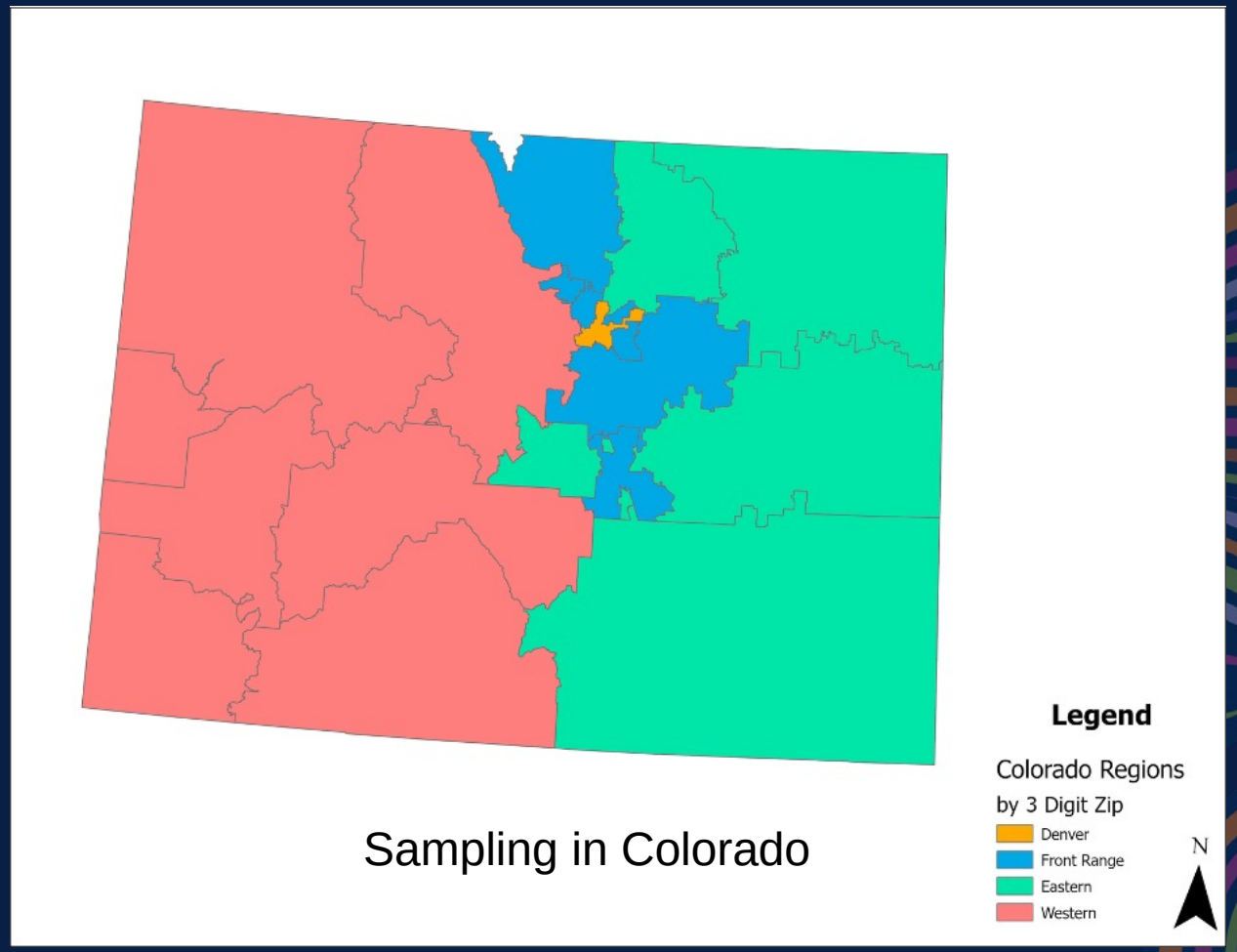

ketamine infusion centers texas
Rating
Hours
All filters
Sign in
Ketamine Clinic of North Texas
3.7 ★★★½☆ (6)
Psychiatric hospital · 4100 Fairway Dr #200
Open · Closes 5:30 PM · (972) 221-1741
Website
Directions
"He treated me with Ketamine infusions, and the results were incredible."
Ketamine Health & Wellness Center of Texas
4.7 ★★★★½ (55)
Mental health service · 5944 W Parker Rd #400
Open · Closes 8 PM · (972) 212-4341
Website
Directions
"I did my research and checked out a few infusion choices."
Lone Star Infusion - Ketamine in Houston
5.0 ★★★★★ (87)
Medical clinic · 14740 Barryknoll Ln #140
Closes soon · 4 PM · Opens 6 AM Tue · (281) 719-9300
Website
Directions
"Grateful my path led me to lone star infusion."
Houston Ketamine Center -
Ketamine Infusion Clinic of El Paso
Ketamine Care Clinic
Elevate Infusion Therapy...
Ketamine Therapy Texas
Ketamine Infusion Treatment Center
Sugar Land Ketamine Infusion...
Albuquerque
Santa Fe
Amarillo
Lubbock
Odessa
Abilene
Waco
Tyler
Shreveport
Jackson
Tucson
Sierra Vista
Hobbs
Carlsbad
Roswell
Alamogordo
Clovis
Gallup
Durango
Pueblo
Dodge City
Wichita
Joplin
Springfield
Branson
Tulsa
Norman
Conway
Memphis
Jonesboro
New Orleans
Corpus Christi
Nuevo Laredo
Monclova
Piedras Negras
Ojinaga
Chihuahua
Ciudad Juárez
Delicias
Camargo
Parral
Ciudad Obregón
Navojoa
Hermosillo
Los Mochis
Guasave
Guamúchil
Torreón
Saltillo
Monterrey
Reynosa
Matamoros
KANSAS
MISSOURI
OKLAHOMA
ARKANSAS
LOUISIANA
MISSISSIPPI
TEXAS
NEW MEXICO
COAHUILA
NUEVO LEON
CHIHUAHUA
SONORA
NAVAJO NATION
NAVAJO NATION OFF-RESERVATION TRUST LAND
FORT APACHE RESERVATION
CHEROKEE NATION
CHOCTAW NATION
CHICKASAW NATION
Gila National Forest
Gulf of

Small Area Estimation Allows Assessment of Regional Availability

- All data sources divided based on 3-digit ZIP codes reported by respondents or patients
- Aggregations preserve privacy according to HIPAA compliance

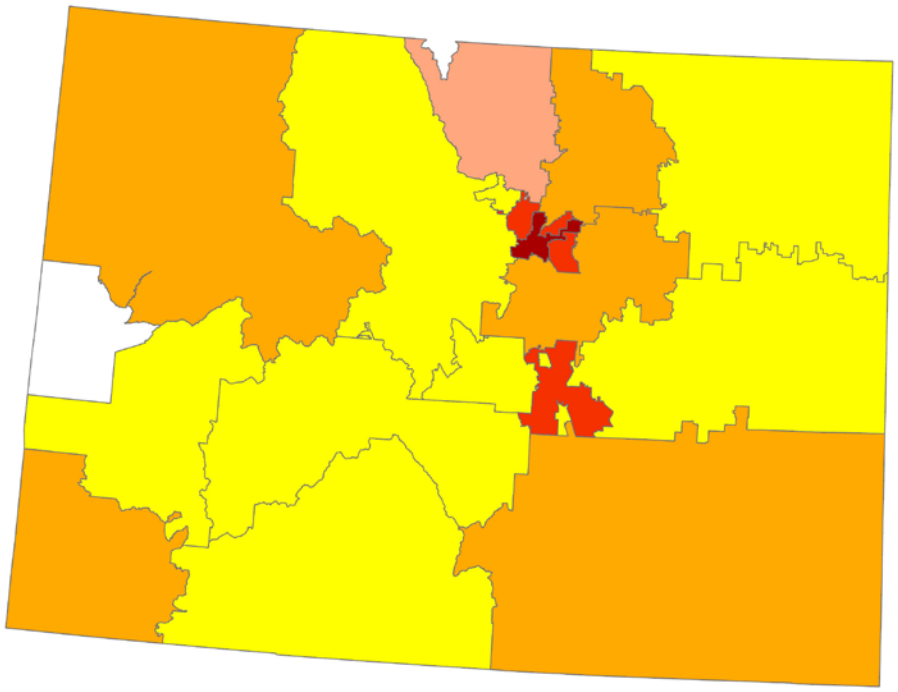


Sampling in Colorado

Fentanyl Exposure Origin and Reasons: Poison Center

	Intentional, N, (%)	Unintentional, N, (%)	Unknown/ Other, N, (%)
Denver	32 (72.3)	6 (13.6)	6 (13.6)
Front Range	53 (75.7)	11 (15.7)	6 (8.6)
Eastern	10 (83.3)	1 (8.3)	1 (8.3)
Western	9 (56.2)	5 (31.2)	2 (12.5)

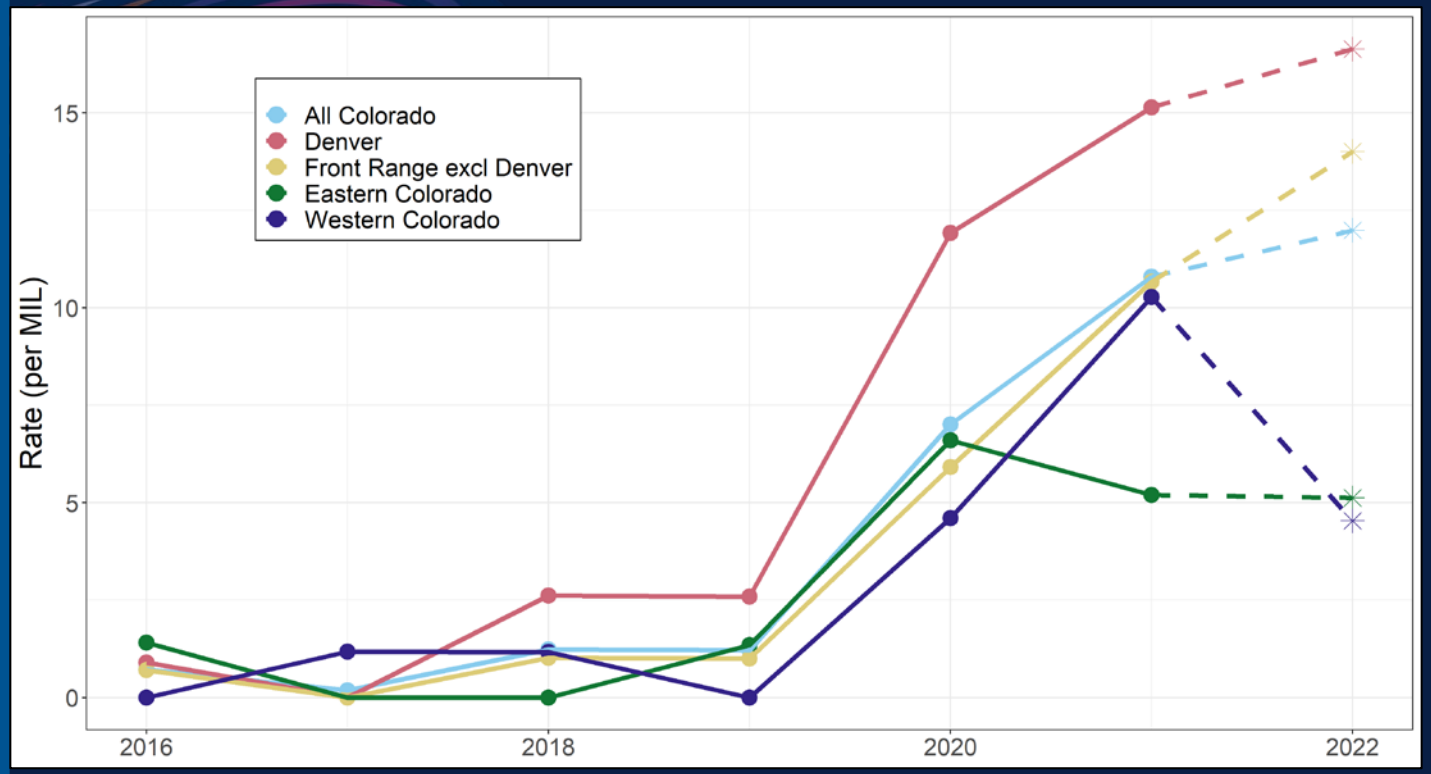
Most exposures to Poison Centers are Intentional, similar across all regions. Potentially higher unintentional rate in Western region



Poison Center Reporting in Colorado

Thanks to Joshua Black for this slide

Fentanyl Use in Denver vs Other Colorado Regions



*Indicates projected value, Western and Eastern Colorado upon small case #s

Region	Rate Ratio	P-value
Denver	REF	--
Front Range	0.61 (0.36-1.03)	0.0639
Eastern	0.42 (0.24-0.76)	0.0042
Western	0.49 (0.28-0.86)	0.0129

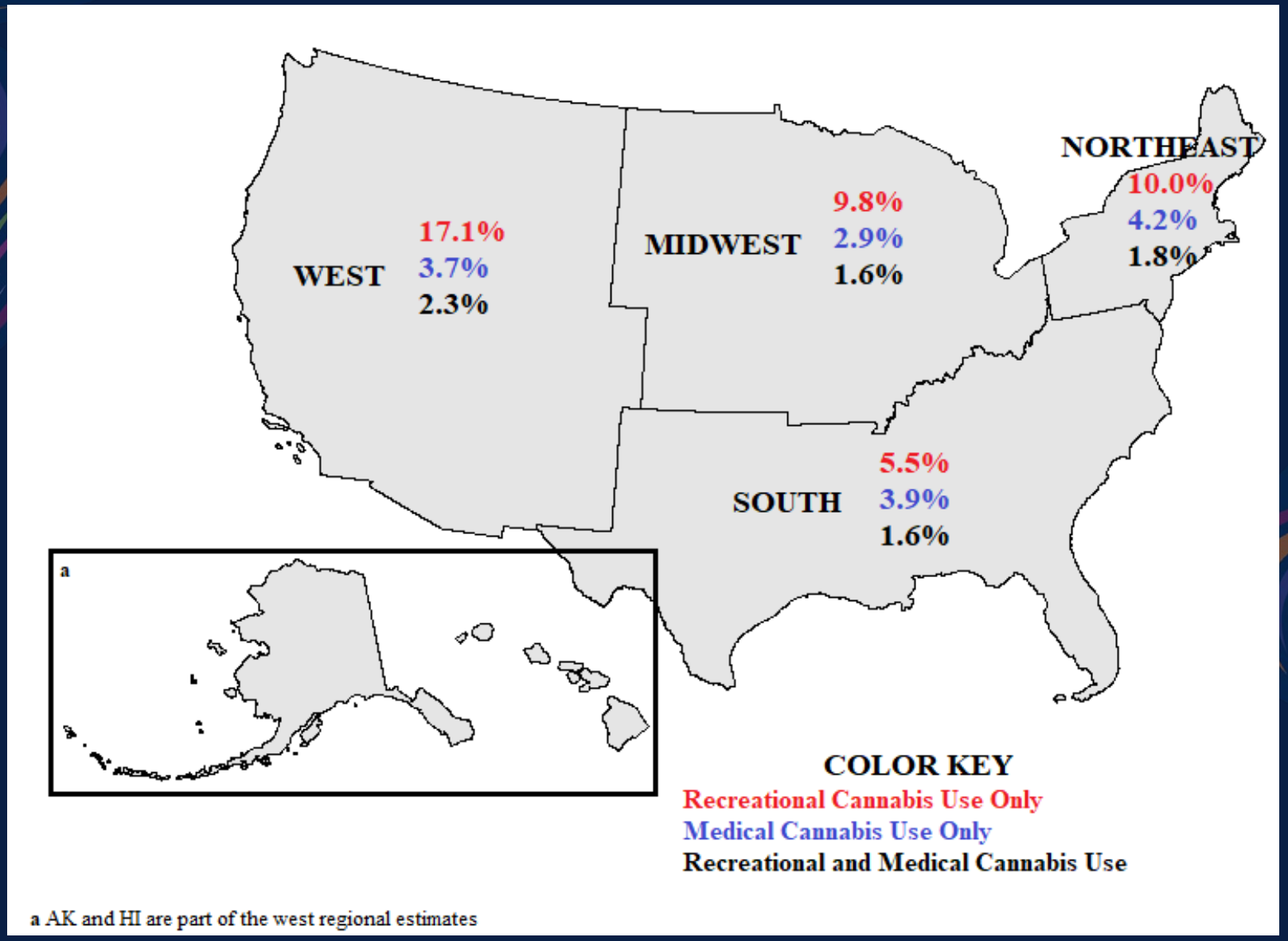
Cumulative rate of fentanyl exposure is estimated to be approximately **2X** higher than other Colorado regions.

Thanks to Joshua Black for this slide

Necessary Surveillance Components for These Drugs

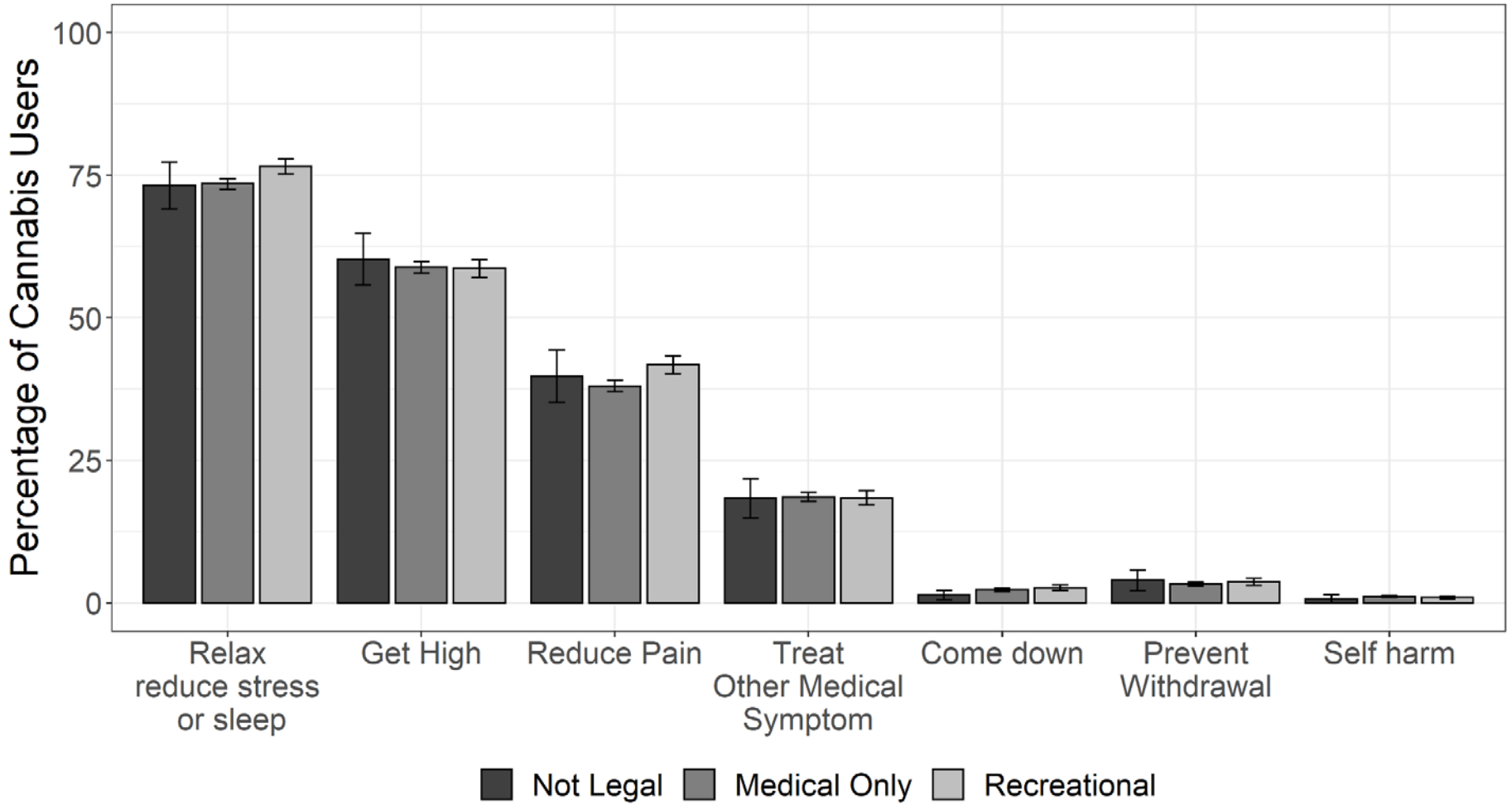
- Small area assessment
- Assessment of use patterns for both approved and illicit products

Cannabis Use Patterns by US Region

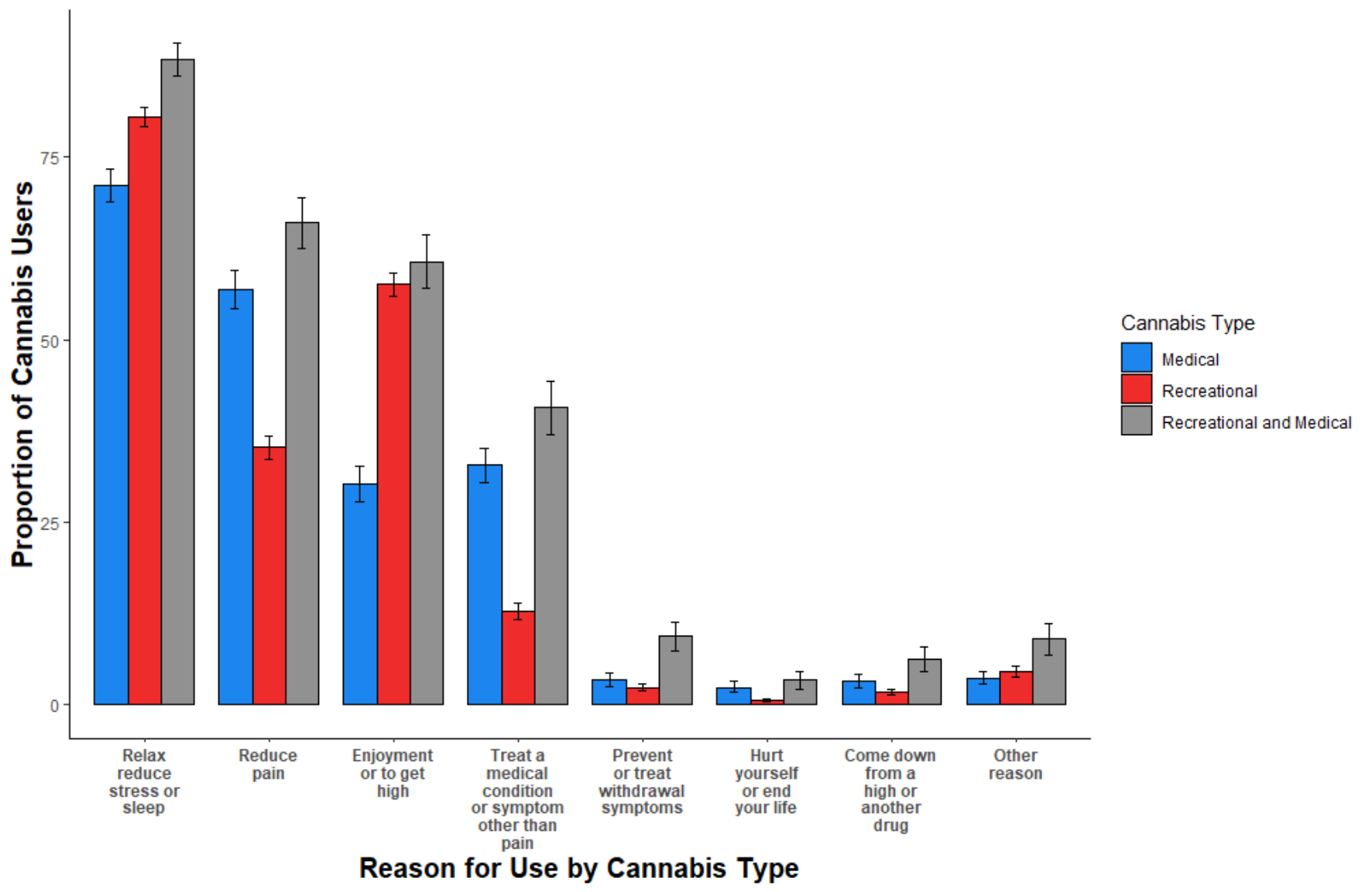


a AK and HI are part of the west regional estimates

Cannabis Users Use for the Same Reasons Regardless of State Policy

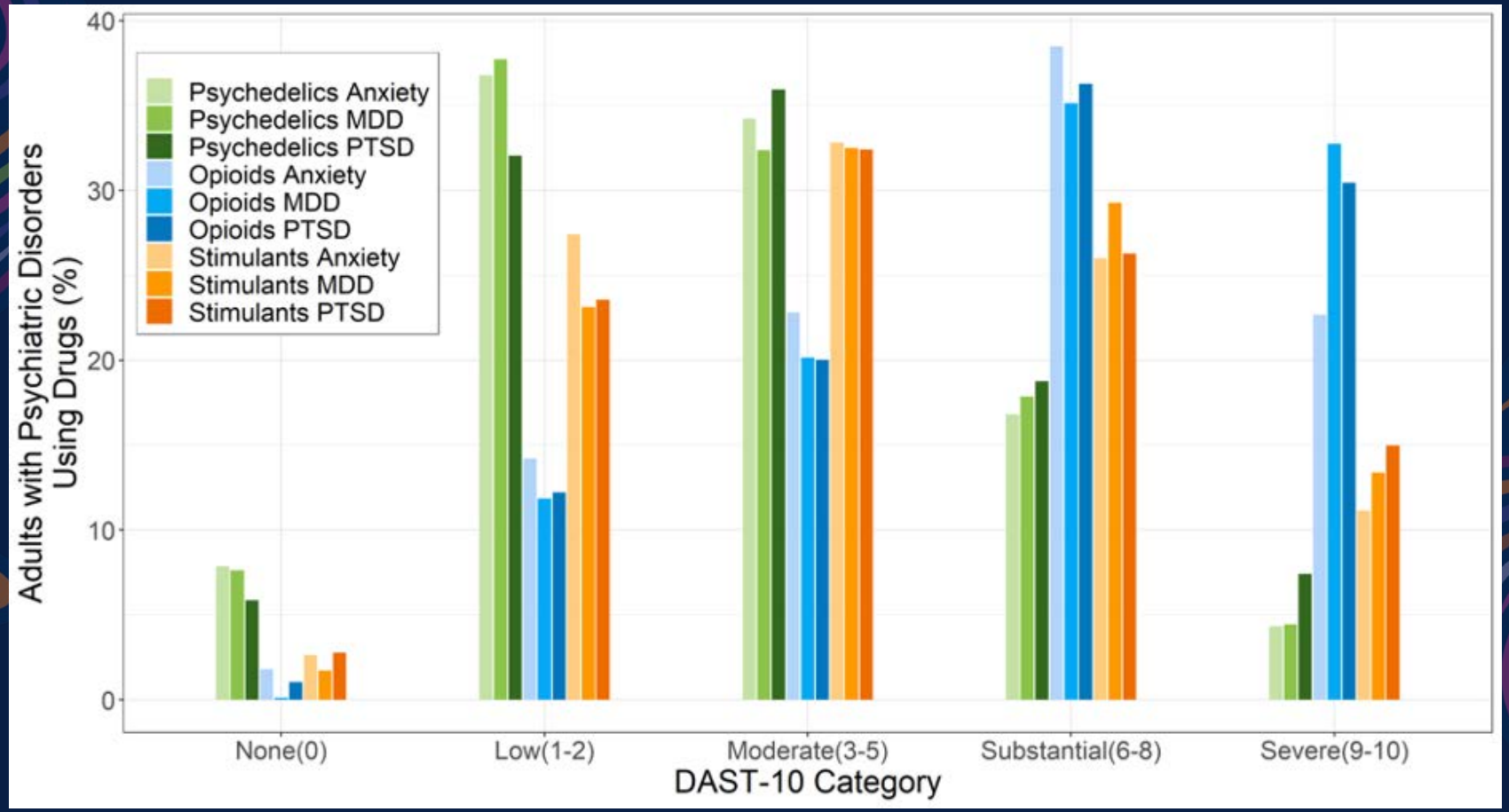


Reason for Use Varies by Source



Understanding why allows interpretation, and targets mitigation of adverse events.

Problematic Substance Abuse is Lower in Psychedelic Users Compared to Opioid or Stimulant Users



Thanks to Joshua Black for this figure

Increased availability will lead to increased reports of adverse events. We must be specific about the products we monitor.


Original Investigation
Pediatric Marijuana Exposures in a
George Sam Wang, MD; Genie Roosevelt, MD, MPH; Kennon Heard
IMPORTANCE
Original Investigation
Medical Cannab
Mortality in the Uni
Marcus A. Bachhuber, MD; Brendan Saloner, PhD; Chinazo
Opioid Analgesic Overdose
09-2010
Medical Marijuana Laws and Suicides by Gender and Age
D. Mark Anderson, PhD, Daniel I. Rees, PhD, and Joseph J. Sabia, PhD
The Effect of Medic
aws on Crime: Evidence
from State Panel Data,
Robert G. Morris*, Michael TenEyck, J. C. Barnes,
MAIN EXPOSURE Marijuana ingestion
MAIN OUTCOMES AN
and patien
CO
ONS AND RELEVANCE
ingestions by young children after modification of drug enforcement laws for marijuana
possession in Colorado. The consequences of unintentional marijuana exposure in children
should be part of the ongoing debate on legalizing marijuana.
sive care unit. Eight of the 14 cases involved medical
posures were from food products.
Author Affiliations: Rocky Mountain
Poison and Drug Center, Denver
Health, Denver, Colorado (Wang,
Heard); Department of Pediatric
Section of Emergency M
University of Co
Medic

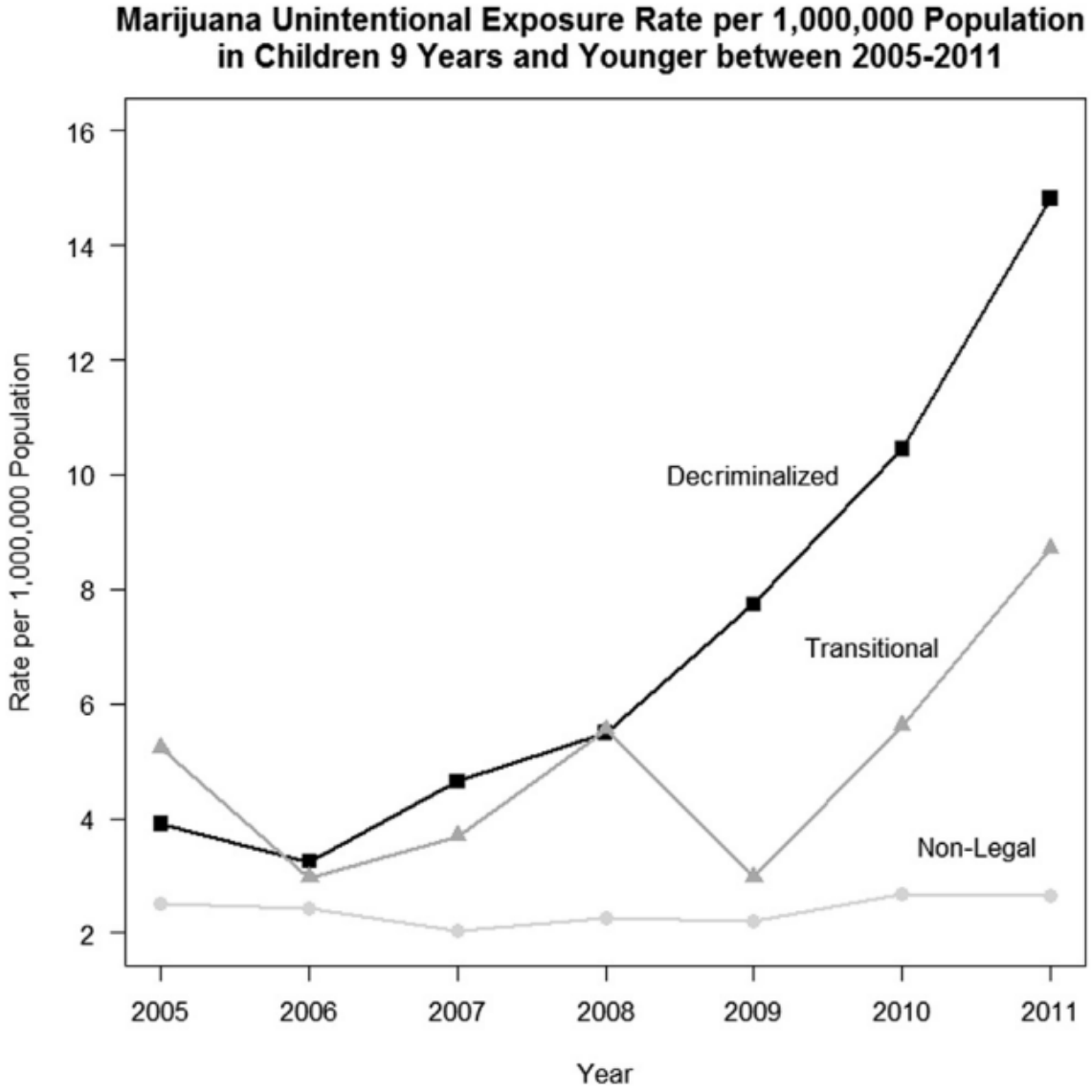
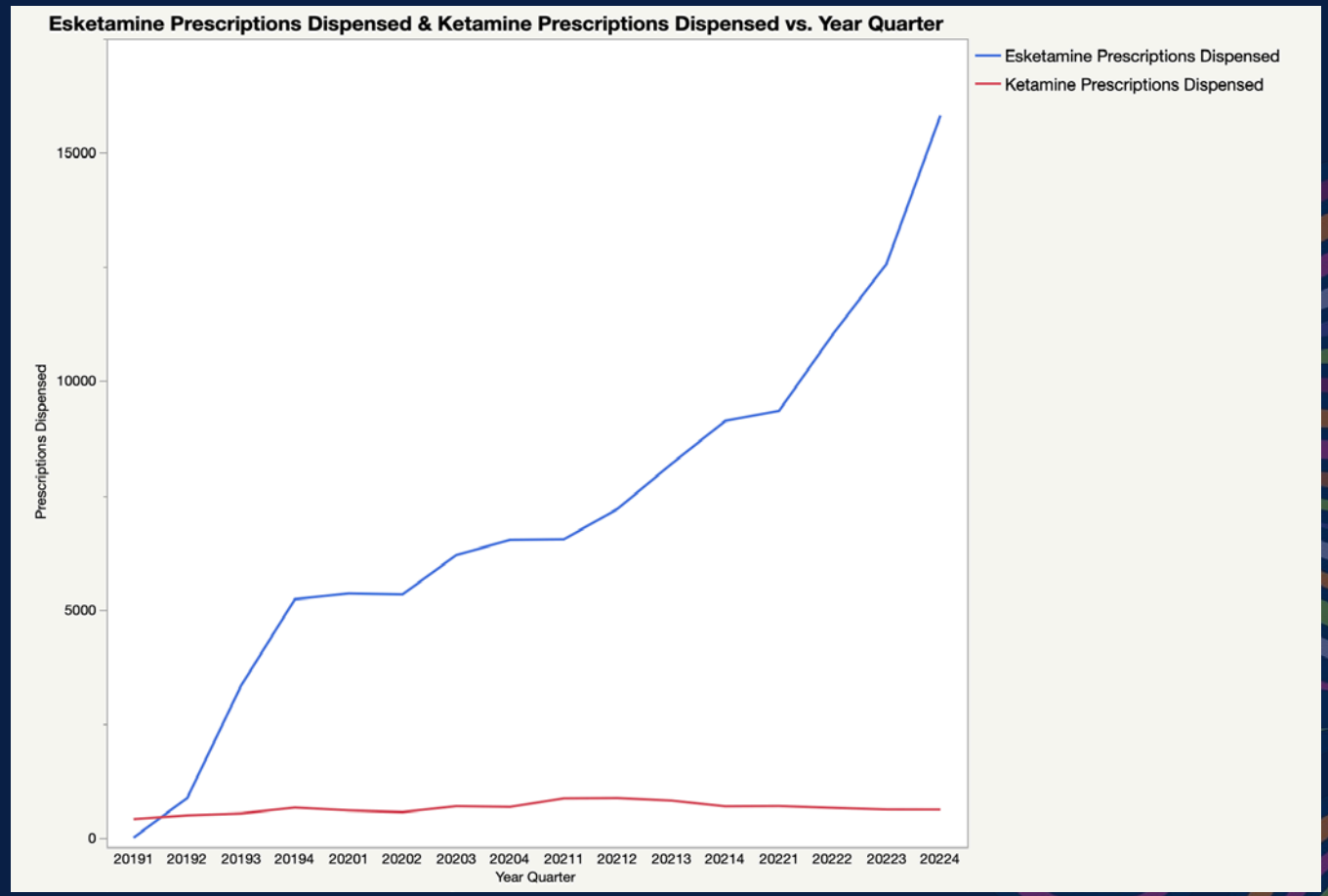


Figure 2. Comparison of unintentional marijuana exposure rates between nonlegal, transitional, and decriminalized states.

Wang, Acad EM. 2014

Esketamine vs Ketamine

- Rxs of esketamine have increased rapidly comparatively.
- Mis-classification hinders tracking of patient reports
- Illicit and diverted drugs may show up from different sources.
- We would expect to see an increase in ADEs as Rx increase.



IQVIA Longitudinal Rx Data

Esketamine vs Ketamine: 2019-2022

Data Source	Esketamine	Ketamine
Poison Center Abuse+ Misuse Reports	1	406
Treatment Center Abuse Reports	17	359
Diversion Reports	1	46
Street Rx Reports	N/A	44

Necessary Surveillance Components for These Drugs

- Small area assessment
- Assessment of use patterns for both approved and illicit products
- Assessment of effectiveness

Assessment of effectiveness allows understanding of the risk benefit ratio and which groups are at highest risk.

Maximize availability while minimizing risk.

Rate of AEs Depends Upon Reasons for Use

- Systematic review
- Nausea in cancer patients
- THC effective for nausea
- Moderate efficacy, and very few AEs

Study (Reference)	Dosage and Form of THC	Patients	Design	Patient Age	Results
		n		*y*	
Sallan et al. (4)	15 mg or 10 mg/m² body surface area orally every 4 hours for 3 days	10	Randomized, double-blind, cross-over	29.5†	THC better than prochlorperazine
Sallan et al. (5)	10 mg/m² orally every 4 hours for 3 days	46	Randomized, double-blind, cross-over	32.5‡	THC better than prochlorperazine
Chang et al. (6)	10 mg/m², orally and smoked, every 3 hours for 5 days	15	Randomized, cross-over	24†	THC better than prochlorperazine
Frytak et al. (7)	15 mg orally	116	Prospective, double-blind	61†	THC equal to prochlorperazine and both drugs better than placebo
Kluin-Neleman et al. (8)	10 mg/m² orally	11	Double-blind, cross-over	34.6†	THC better than placebo
Ekert et al. (9)	10 mg/m² orally compared with metoclopramide	33	Double-blind, cross-over	5–19	THC better than prochlorperazine or oral metoclopramide
Lucas and Laszlo (10)	5–15 mg/m² orally every 4–6 hours 24 hours after chemotherapy	53	Randomized, cross-over	Adults	THC effective
Orr et al. (11)	7 mg/m² orally every 4 hours for 3 days	55	Randomized, double-blind, cross-over	46‡	THC better than prochlorperazine and both drugs better than placebo
Gralla et al. (12)	10 mg/m² orally every 3 hours for 5 days compared with intravenous metoclopramide	27	Randomized, double-blind	Adults	Metoclopramide better than THC
Ungerleider et al. (13)	7.5–12.5 mg orally	214	Randomized, double-blind, cross-over	47‡	THC equal to prochlorperazine
Levitt et al. (14)	Oral THC and smoked marijuana	20	Randomized, double-blind	54.5‡	Oral THC better than smoked THC
Vinciguerra et al. (15)	Approximately 5 mg of smoked marijuana per m²	56	Prospective, uncontrolled	40‡	Smoked THC effective; no controls used
Lane et al. (16)	10 mg oral THC plus prochlorperazine	60	Randomized, double-blind	55‡	Combination more effective than individual drugs

* THC = delta-9-tetrahydrocannabinol.
† Median age.
‡ Mean age.

Voth, et al. Ann Int Med. 1997.

Rate of AEs Depends Upon Reasons for Use

- Systematic review/meta analysis
- 18 double blind RCTs in chronic pain
- Synth derivatives included
- VAS outcomes, captured AEs
- Moderate efficacy, but risks may outweigh benefits

OUTCOME	OR (95% CI)
Intensity of pain	**-0.61 (-0.84, -0.37)**
Euphoria	**4.11 (1.33, 12.72)**
Dysphoria	2.56 (0.66, 9.92)
Blurred vision	**8.34 (4.63, 15.03)**
Tinnitus	2.18 (0.93, 5.11)
Disorientation/Confusion	**3.24 (1.51, 6.97)**
Dissociation/ Acute psychosis	3.18 (0.89, 11.33)
Speech disorders	**4.13 (2.08, 8.20)**
Ataxia, muscle twitching	**3.84 (2.49, 5.92)**
Numbness	**3.98 (1.87, 8.49)**
Impaired memory	**3.45 (1.19, 9.98)**
Attention disturbances	**5.12 (2.34, 11.21)**

Martin-Sanchez. Pain Med. 2009

ASSESSMENT OF BOTH EFFECTIVENESS AND SAFETY

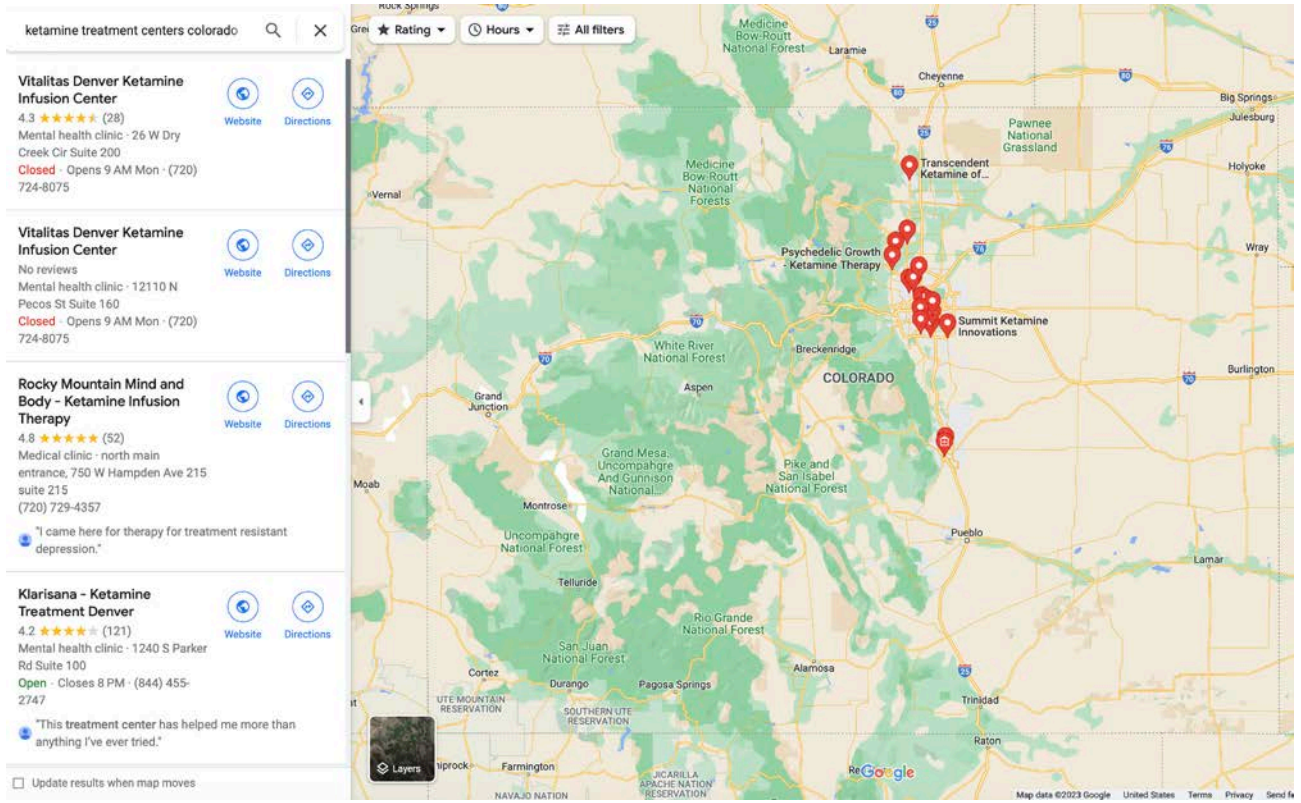
- Adverse event rates are different in populations where the drug is effective vs not.
- Integration of validated tools to measure effectiveness
  - SF-12 (Short Form Health Survey)
  - PHQ-8 (Quick Depression Assessment)
  - 100 mm VAS (Pain)
  - Davidson Trauma Scale (PTSD)

Necessary Surveillance Components for These Drugs

- Small area assessment
- Assessment of use patterns for both approved and illicit products
- Assessment of effectiveness
- Therapeutic and treatment center monitoring

Therapeutic vs Substance Abuse Treatment Centers for Psychedelics

- The therapeutic center environment may alter effectiveness and safety.
- Substance abuse treatment centers help assess emerging problems.



Gaps Remain: Hidden Populations

- Psychedelic treatment centers (both therapeutic and substance abuse treatment centers)
- Low prevalence behaviors/populations are difficult to surveil
- Flexibility of tools remains key

Cannabinoid Hyperemesis Syndrome

- Gastrointestinal symptoms are the most common reason patients come to the ED for cannabis attributable complaints.
- 84.9% of those visits are CHS.
- CHS is almost entirely observed in inhalational users.
- Median cost if CHS ED visits & hospital admissions: $95,023 (IQR: $62,420-$268,110)

Shelton, et al. Clin Tox. 2019, Perrotta, et al. Acad Emer Med, 2012.

Finding Hidden Populations

- Cannabinoid hyperemesis syndrome (CHS)?
- What is the prevalence?
- What is the incidence?
- How many health care visits are associated with CHS?

Things we didn’t know, things we don’t know. . .

Cannabis

- Edibles lead to 33 times more ED visits proportionally
- Patients use for the same reasons, regardless of policy
- Use increases in cannabis legal states, but problematic use does not increase proportionally.
- Cannabinoid hyperemesis syndrome

Psychedelics

- Will there be diversion given availability in the illicit market?
- How different will the therapeutic centers be?
- How much the organic market drive therapy?

Vs.

Monte AA, et al. Ann Int Med, 2019

Complexity Requires Detailed Assessments Across Numerous Tools

- Nationally representative drug use data to understand interaction between substances
- Focused surveys on specific classes (cannabinoids, psychedelics, etc)
- Objective non-self report data (Poison Center, hospitalization, dispensing)
- Product specific stratification
- On-going literature assessments

RMPDS Plans to Fill Gaps

- General Online Longitudinal Drug Survey (GOLDS)
  - Patterned longitudinal data predict long term trajectory (Joshua Black, PhD)
- Increased sampling
- Content specific surveys
- Real time surveillance triggers
- New data sources: Therapeutic center monitoring

Summary

- Unregulated use may be associated with higher AE rates
- Increased availability leads to increased ADE frequency, but that doesn’t tell us rates
- Active and passive surveillance methods are necessary
- Mosaic allows flexibility in a rapidly evolving market
- Data can help to maximize availability and minimize risk


reservationatdorsia.tumblr.com

Panel Discussion and Summary

Richard C. Dart, MD, PhD (Moderator)
Executive Director – RADARS® System, Rocky Mountain Poison & Drug Safety, Denver Health and Hospital Authority
President, Canadian Consumer Product and Pharmaceutical Safety Inc.