Satisfying the Craving for Novel Psychoactive Post-Market Surveillance

Andrew A. Monte, MD, PhD
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

1st Product Market Available

Premarket Landscape
- Population of potential patients
- Patient qualification for treatment
- Symptomatology of people currently using
- Public health burden

Low & Increasing Volume
- Effectiveness as modified by factors (e.g., determinants)
- Differentiating medical vs recreational use
- Adverse event emergence
- Changing illicit landscape
- National prevalence

Mature Volume
- Real-world causal understanding of effectiveness and adverse events
- Differences in effectiveness for subpopulations
- Prevalence of health burden
- Multiple product emergence

Clinical Trials Complete

Time

Thanks to Joshua Black for this slide
Necessary Surveillance Components for These Drugs

• Small area assessment
Psychedelic use has increased in liberalized states

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

Data from NMURx Survey
<table>
<thead>
<tr>
<th>Clinic Name</th>
<th>Rating</th>
<th>Reviews</th>
<th>Address</th>
<th>Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitalitas Denver Ketamine Infusion Center</td>
<td>4.3</td>
<td>28</td>
<td>26 W Dry Creek Cir Suite 200</td>
<td>(720) 724-8075</td>
</tr>
<tr>
<td>Vitalitas Denver Ketamine Infusion Center</td>
<td>4.6</td>
<td>52</td>
<td>12110 N Pecos St Suite 160</td>
<td>(720) 729-4357</td>
</tr>
<tr>
<td>Rocky Mountain Mind and Body - Ketamine Infusion Therapy</td>
<td>4.6</td>
<td>52</td>
<td>750 W Hampden Ave 215 suite 215</td>
<td>(720) 724-8075</td>
</tr>
<tr>
<td>Klarisana - Ketamine Treatment Denver</td>
<td>4.2</td>
<td>121</td>
<td>1240 S Parker Rd Suite 100</td>
<td>(844) 455-2747</td>
</tr>
</tbody>
</table>

Reviews:
- Rocky Mountain Mind and Body: "I came here for therapy for treatment resistant depression."
- Klarisana: "This treatment center has helped me more than anything I've ever tried."
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
Poison Center Reporting in Colorado

<table>
<thead>
<tr>
<th>Region</th>
<th>Intentional, N, (%)</th>
<th>Unintentional, N, (%)</th>
<th>Unknown/Other, N, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denver</td>
<td>32 (72.3)</td>
<td>6 (13.6)</td>
<td>6 (13.6)</td>
</tr>
<tr>
<td>Front Range</td>
<td>53 (75.7)</td>
<td>11 (15.7)</td>
<td>6 (8.6)</td>
</tr>
<tr>
<td>Eastern</td>
<td>10 (83.3)</td>
<td>1 (8.3)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Western</td>
<td>9 (56.2)</td>
<td>5 (31.2)</td>
<td>2 (12.5)</td>
</tr>
</tbody>
</table>

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

Thanks to Joshua Black for this slide
Fentanyl Use in Denver vs Other Colorado Regions

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

<table>
<thead>
<tr>
<th>Region</th>
<th>Rate Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denver</td>
<td>REF</td>
<td>--</td>
</tr>
<tr>
<td>Front Range</td>
<td>0.61</td>
<td>0.0639</td>
</tr>
<tr>
<td></td>
<td>(0.36-1.03)</td>
<td></td>
</tr>
<tr>
<td>Eastern</td>
<td>0.42</td>
<td>0.0042</td>
</tr>
<tr>
<td></td>
<td>(0.24-0.76)</td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>0.49</td>
<td>0.0129</td>
</tr>
<tr>
<td></td>
<td>(0.28-0.86)</td>
<td></td>
</tr>
</tbody>
</table>

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

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 Users Use for the Same Reasons Regardless of State Policy
Reason for Use Varies by Source

![Bar chart showing the proportion of cannabis users by reason and cannabis type.](chart_image)
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.
Medical Marijuana Laws and Suicides by Gender and Age

Pediatric Marijuana Exposures in a Medicaid-Insured Population

Medical Cannabis Mortality in the United States: 209-2010


Robert G. Morris, Michael TenEyck, J. C. Barnes, Marcus A. Bachhuber, MD, Brendan Saloner, PhD, Chinazonu Amenze, MPH
Figure 2. Comparison of unintentional marijuana exposure rates between nonlegal, transitional, and decriminalized states.

Wang, Acad EM. 2014
• 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.
### Esketamine vs Ketamine: 2019-2022

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Esketamine</th>
<th>Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poison Center Abuse+ Misuse Reports</td>
<td>1</td>
<td>406</td>
</tr>
<tr>
<td>Treatment Center Abuse Reports</td>
<td>17</td>
<td>359</td>
</tr>
<tr>
<td>Diversion Reports</td>
<td>1</td>
<td>46</td>
</tr>
<tr>
<td>Street Rx Reports</td>
<td>N/A</td>
<td>44</td>
</tr>
</tbody>
</table>
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
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

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

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)

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?

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
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.