TREATING CHRONIC PAIN AND SUBSTANCE USE DISORDERS: THE ROLE OF OPIOIDS AND CANNABIS

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Acknowledgements and Disclosures

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  - National Institute on Drug Abuse
  - Department of Veterans Affairs

- **Conflicts**
  - Arborsense
  - No other conflicts of interest
Improving outcomes for pain and addiction

- Medical Cannabis
- Substances Use Disorders (SUDs)
- Pain
- Rx Opioid Misuse
Overview – pain and addiction

- The overlap between pain and Substance Use Disorders (SUDs)
- Opioids and opioid-related adverse outcomes
- Strategies to address overuse of opioids
- Medical Marijuana
- Treatments to address chronic pain in those with SUDs
Overlap between chronic pain and SUDs

- In community samples pain is associated with increased risk of SUDs – mainly alcohol use disorders (Von Korff et al., 2005).
- Pain in those with SUDs in VHA patients (N = 5,195,551; unpublished):
  - Among those with an SUD:
    - 44.5% with arthritis (OR = 1.55; 1.54 -1.56)
    - 32.0% with back pain (OR = 2.00; 1.99 - 2.02)
    - 5.6% with neuropathic pain (OR = 1.39; 1.37 - 1.41)
    - 2.1% with migraine (OR = 1.43; 1.40 - 1.47)
- SUDs in specialty pain care (Morasco et al., 2011):
  - Up to 30% of patients have a current SUD
- Rates of pain in SUD treatment settings (Potter et al., 2010):
  - ~50% or more of patients in addictions treatment report pain
Pain sensations in the body
Overlapping physiology related to pain and addiction

From Volkow 2017 presentation; Egli, Koob, & Edwards. 2012
Fear Avoidance Model of Chronic Pain

- Pain Perpetuation and Exit Strategy

- Avoidance/Substance Use
  - Fear of movement/re-injury
  - Catastrophizing

- Disability
  - Depression
  - SUD

- Injury

- Painful experiences

- Recovery
  - Confrontation
    - Avoidance
    - Substance Use

- Non-Catastrophizing
Why do pain and SUDs overlap?

Issues specific to opioids:

- Tolerance - not the same as OUD
- Hyperalgesia
Methadone maintenance patients: pain sensitivity (CPT)

https://archives.drugabuse.gov/meetings/apa/ppt/ling.ppt
Opioid-related adverse outcomes
THE OPIOID EPIDEMIC
A Generation in Crisis
Rates of prescription painkiller sales, deaths and SUD treatment admissions (1999-2010)

Figure 1
Overdose Death Rates

1999

2015

2008-2014, Utah
Death Rates per 100,000 Population
Poisoning, All Intents, All Races, All Ethnicities, Both Sexes, Ages 15-75 Years
Annualized Crude Rate for Utah: 29.40

Reports for All Ages include those of unknown age.
* Rates based on 20 or fewer deaths may be unstable. These rates are suppressed for counties (see legend above); such rates in the title have an asterisk.

https://www.cdc.gov/injury/wisqars/fatal.html
Is overdose risk related to dose of medication?

Bohnert ASB, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, Blow FC. The association between opioid prescribing patterns and opioid overdose-related deaths. JAMA, 305, 1315-1321 2011
Risk of Unintentional Overdose for SUDs

What can be done to address risky opioid prescribing?

System-level responses
System-level responses to opioid crisis

- Narcan (naloxone) distributed to reduce overdose death.
  - Data support these efforts but most published results are based on injection drug users
- State Prescription Drug Monitoring Programs
- Policy changes within large health systems
## PDMPs and overdose

### Table: Associations between use and features of prescription drug monitoring programs (PDMPs) and opioid-related overdose death rates, 1999–2013

<table>
<thead>
<tr>
<th>EXPLANATORY VARIABLES</th>
<th>Unadjusted Deaths</th>
<th>95% CI</th>
<th>Model 1 (adjusted) Deaths</th>
<th>95% CI</th>
<th>Model 2 (adjusted) Deaths</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDMP implementation</td>
<td>2.35****</td>
<td>1.91, 2.80</td>
<td>-1.12****</td>
<td>-1.68, -0.55</td>
<td>-0.18</td>
<td>-0.65, 0.28</td>
</tr>
<tr>
<td>Interaction of PDMP implementation with time</td>
<td>0.62****</td>
<td>0.52, 0.73</td>
<td>0.11*</td>
<td>0.00, 0.23</td>
<td>-0.11**</td>
<td>-0.20, -0.02</td>
</tr>
<tr>
<td>Four or more drug schedules monitored</td>
<td>1.76****</td>
<td>1.19, 2.32</td>
<td></td>
<td></td>
<td>-0.55**</td>
<td>-1.02, -0.08</td>
</tr>
<tr>
<td>Data updated at least weekly</td>
<td>1.76****</td>
<td>1.31, 2.21</td>
<td></td>
<td></td>
<td>-0.82****</td>
<td>-1.25, -0.38</td>
</tr>
<tr>
<td>Mandatory use or registration</td>
<td>2.06****</td>
<td>1.25, 2.88</td>
<td></td>
<td></td>
<td>0.30</td>
<td>-0.27, 0.87</td>
</tr>
</tbody>
</table>

### Table: State-level and time-trend controls

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Deaths</th>
<th>95% CI</th>
<th>Model 1 (adjusted) Deaths</th>
<th>95% CI</th>
<th>Model 2 (adjusted) Deaths</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDMP legislation enactment</td>
<td>2.66****</td>
<td>2.28, 3.04</td>
<td>0.17</td>
<td>-0.40, 0.74</td>
<td>-0.08</td>
<td>-0.47, 0.31</td>
</tr>
<tr>
<td>Educational attainment</td>
<td>1.06****</td>
<td>0.95, 1.16</td>
<td>-0.08</td>
<td>-0.40, -0.24</td>
<td>-0.08</td>
<td>-0.30, 0.15</td>
</tr>
<tr>
<td>Unemployment rate</td>
<td>0.59****</td>
<td>0.49, 0.70</td>
<td>-0.08</td>
<td>-0.19, 0.03</td>
<td>0.00</td>
<td>-0.08, 0.07</td>
</tr>
<tr>
<td>Linear time trend</td>
<td>0.37****</td>
<td>0.34, 0.40</td>
<td>0.43****</td>
<td>0.33, 0.52</td>
<td>0.46****</td>
<td>0.36, 0.55</td>
</tr>
</tbody>
</table>

Patrick et al., *Health Affairs*, 2016
VHA’s Opioid Safety Initiative (OSI)

- Four key targets of the OSI:
  - The number of patients prescribed opioids
  - The average dose per day per drug
  - The number of patients prescribed both opioids and sedatives
  - The number of fentanyl patches dispensed

- Focus is on prescribing (measurable w/ PBM data)
- Limited discussion of ‘how?’ – this is left to the facilities
- Newer emphasis on increasing use of UDS, State PDM databases, knowledge of tapering strategies, use of behavioral medicine services and CAM
OSI evaluation (>200 MEQ daily)

Lin, Bohnert, Kerns, Clay, Ganoczy, Ilgen. (in press). PAIN
What can be done to address risky opioid prescribing?

Medical Marijuana Legalization
Legalizing cannabis to reduce burdens associated with opioids

**Original Investigation**

**Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010**

Marcus A. Bachhuber, MD; Brendan Saloner, PhD; Chinazo O. Cunningham, MD, MS; Colleen L. Barry, PhD, MPP


**State Medical Marijuana Laws and the Prevalence of Opioids Detected Among Fatally Injured Drivers**

June H. Kim, MPhil, MHS, Julian Santaella-Tenorio, DVM, MSc, Christine Mauro, PhD, Julia Wrobel, MS, Magdalena Cerdà, DrPH, Katherine M. Keyes, PhD, Deborah Hasin, PhD, Silvia S. Martins, PhD, and Guohua Li, MD, DrPH
Studies of cannabis for pain relief

- The Institute of Medicine (2009) noted the preliminary nature of support for the potential medical uses of cannabinoids and encouraged more research.
- Meta-analysis of 18 double-blind controlled trials indicating that increased dose of cannabis is associated with greater reduction in pain (Martín-Sánchez et al., 2003). Noted adverse events: altered motor functioning, cognitive functioning, altered perceptions.
- Other “Positive” Studies
  - Ware et al CMAJ 2010 – 5 days
  - Ellis et al Neuropsychopharmacology 2009 -5 days
  - Wilsey et al The Journal of Pain 2008 – 1 day
Effects on pain threshold and tolerance

Woodward et al., 1988

<table>
<thead>
<tr>
<th>Table I</th>
<th>Mean differences in threshold and tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean threshold effect *</td>
</tr>
<tr>
<td></td>
<td>Standard error</td>
</tr>
<tr>
<td></td>
<td>Mean tolerance effect *</td>
</tr>
<tr>
<td></td>
<td>Standard error</td>
</tr>
</tbody>
</table>
Marijuana as Analgesic based on laboratory studies

- Fairly consistent evidence for short-term effect of cannabis use on reduced pain
- Key questions remain unanswered about:
  - Route of administration
  - Potency, dose
  - Strain
- Some reported harms
- Not clear how well any of this translates into the real world:
  - Regular use vs. short-term use
  - Impact on functioning
Consequences in recreational users

- No apparent risk of fatal overdose!
- Short term memory problems (limited)
- Increased risk of psychotic disorders (controversial: marker vs. causal effects; see Valmaggia et al., 2014)
- Psychosocial and Functional Impairment
  - Lower grades, school dropout, use of other illicit drugs, crime, and unemployment (Addiction 2002:97:1123)
  - Increased Negative life events
  - Car accidents “The pooled risk of a MVA while driving under the influence of cannabis was almost twice the risk (OR 1.96) of driving unimpaired.” (BMJ February 9, 2012)
  - Decreased workplace productivity (Lehman and Simpson, 1992)
DSM-V (APA) definition of a substance use disorder

- Taking the substance in larger amounts or for longer than the you meant to
- Wanting to cut down or stop using the substance but not managing to
- Spending a lot of time getting, using, or recovering from use of the substance
- **Cravings and urges to use the substance**
- Not managing to do what you should at work, home or school, because of substance use
- Continuing to use, even when it causes problems in relationships
- Giving up important social, occupational or recreational activities because of substance use
- Using substances again and again, even when it puts the you in danger
- Continuing to use, even when the you know you have a physical or psychological problem that could have been caused or made worse by the substance
- **Needing more of the substance to get the effect you want (tolerance)**
- Development of withdrawal symptoms, which can be relieved by taking more of the substance.
Cannabis withdrawal

- Withdrawal
  - Use: High → Withdrawal: depressed mood
  - Use: Anxiolytic → Withdrawal: anxiety
  - Use: Sedation → Withdrawal: sleep disruptions
  - Use: Analgesia → Withdrawal: ??? (headaches; hyperalgesia not well documented)

- Cannabis use is an extremely effective treatment for cannabis withdrawal
Medical cannabis use in the US

- Medical use of cannabis has been approved in 29 US States and DC
- The laws vary by state but, they have the following characteristics in common:
  - The individual must have one or more of a set of qualifying conditions
  - A physician documents that the individual has one of these conditions and signs a form that is submitted to the state
  - The state provides a card as verification that a patient can possess marijuana
  - The patient can then either grow a small amount of marijuana or obtain it from a “caregiver”
  - The cards must be renewed to remain valid
Who can provide medical marijuana certification?

- Any physician but... many physicians are reluctant to sign medical marijuana applications → medical marijuana clinics.
Goals of cohort study of medical cannabis patients

- Overall goal of this project (R01 DA033397) is to understand who uses medical cannabis and to understand the relationships between cannabis use, pain and functioning.
- The findings presented today are preliminary.
Overall study design

Screen patients seeking to obtain a medical cannabis card (~1500)

Cohort of 800 adults who use medical cannabis

Follow every 6-months for 2 years (Current Follow-up rate of 88-90% at each time point).
## Demographics (N=1486)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N, %</strong></td>
<td>1486 (100%)</td>
</tr>
<tr>
<td><strong>Male Gender</strong></td>
<td>851 (57%)</td>
</tr>
<tr>
<td><strong>Age (yrs.)</strong></td>
<td></td>
</tr>
<tr>
<td>18-30</td>
<td>250 (17%)</td>
</tr>
<tr>
<td>31-40</td>
<td>351 (24%)</td>
</tr>
<tr>
<td>41-50</td>
<td>315 (21%)</td>
</tr>
<tr>
<td>51-60</td>
<td>369 (25%)</td>
</tr>
<tr>
<td>61 +</td>
<td>201 (14%)</td>
</tr>
<tr>
<td><strong>Caucasian Race</strong></td>
<td>1228 (83%)</td>
</tr>
<tr>
<td><strong>Education: H.S. / GED or less</strong></td>
<td>509 (34%)</td>
</tr>
<tr>
<td><strong>Married / partnered</strong></td>
<td>819 (55%)</td>
</tr>
<tr>
<td><strong>Unemployed</strong></td>
<td>808 (54%)</td>
</tr>
<tr>
<td><strong>Seeking first medical marijuana card</strong></td>
<td>514 (35%)</td>
</tr>
<tr>
<td><strong>Seeking marijuana for pain</strong></td>
<td>1373 (92%)</td>
</tr>
</tbody>
</table>
Changes in Cannabis use over 12-months

<table>
<thead>
<tr>
<th>Frequency of cannabis use</th>
<th>Baseline</th>
<th>6 Mo</th>
<th>12 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>7%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Monthly or less</td>
<td>8%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Weekly</td>
<td>12%</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Daily/almost daily</td>
<td>74%</td>
<td>79%</td>
<td>82%</td>
</tr>
</tbody>
</table>
Changes in opioid use over 12-months

# of Rx opioids used, past 6 months

<table>
<thead>
<tr>
<th>Percent</th>
<th>Baseline</th>
<th>6 Mo</th>
<th>12 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>10%</td>
<td>3%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>20%</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>30%</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>40%</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>50%</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>60%</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Legend:
- None
- 1
- 2 to 3
- 4 +
Changes in Opioid misuse over 12-months

COMM 4-item sum: zero vs. > zero

Baseline: 66% score = 0, 31% score > 0
6 Mo: 75% score = 0, 24% score > 0
12 Mo: 77% score = 0, 21% score > 0
Association between cannabis use and opioid use/misuse over time

<table>
<thead>
<tr>
<th></th>
<th>Cannabis use frequency and quantity at 6-months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MJ qty. /wk., past mo.</td>
</tr>
<tr>
<td><strong>6-mo follow-up</strong></td>
<td></td>
</tr>
<tr>
<td># Rx Opiates used, past 6 mo.</td>
<td>0.04 (-0.04, 0.12)</td>
</tr>
<tr>
<td>Opioid Misuse (COMM sum)</td>
<td>0.02 (-0.06, 0.10)</td>
</tr>
<tr>
<td><strong>12-mo follow-up</strong></td>
<td></td>
</tr>
<tr>
<td># Rx Opiates used, past 6 mo.</td>
<td>0.0 (-0.08, 0.08)</td>
</tr>
<tr>
<td>Opioid Misuse (COMM sum)</td>
<td>-0.03 (-0.11, 0.05)</td>
</tr>
</tbody>
</table>

Spearman Fisher correlations (95% CI): Adjusted for age and Baseline Cannabis use

A p≤0.005; B p≤0.01; C p≤0.05
## Association between cannabis use and pain/functioning over time

<table>
<thead>
<tr>
<th>WHY MPI – Pain severity</th>
<th>6-mo follow-up</th>
<th>12-mo follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>MJ qty. /wk., past mo.</td>
<td>0.09 (0.01, 0.16)</td>
<td>0.09 (0.02, 0.17)</td>
</tr>
<tr>
<td>MMJ freq. (past 6 mo.)</td>
<td>0.09 (0.02, 0.17)</td>
<td>0.04 (-0.04, 0.11)</td>
</tr>
<tr>
<td>WHY MPI – Pain interference</td>
<td>0.13 (0.05, 0.20)</td>
<td>0.11 (0.03, 0.18)</td>
</tr>
</tbody>
</table>

Spearman Fisher correlations (95% CI): Adjusted for age and Baseline Cannabis use

\(A\) \(p < 0.005\); \(B\) \(p < 0.05\); \(C\) \(p < 0.05\)
Association between cannabis use and coping with pain over time

<table>
<thead>
<tr>
<th>6-mo follow-up</th>
<th>Cannabis use frequency and quantity at 6-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Acceptance (CPAQ total)</td>
<td>MJ qty. /wk., past mo.</td>
</tr>
<tr>
<td>-0.08 (-0.16, -0.01)</td>
<td>-0.06 (-0.14, 0.01)</td>
</tr>
<tr>
<td>Self-efficacy (PSEQ sum)</td>
<td>-0.12 (-0.19, -0.04)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12-mo follow-up</th>
<th>Cannabis use frequency and quantity at 6-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Acceptance (CPAQ total)</td>
<td>MJ qty. /wk., past mo.</td>
</tr>
<tr>
<td>-0.10 (-0.18, -0.02)</td>
<td>-0.08 (-0.16, -0.001)</td>
</tr>
<tr>
<td>Self-efficacy (PSEQ sum)</td>
<td>-0.13 (-0.21, -0.05)</td>
</tr>
</tbody>
</table>

Spearman Fisher correlations (95% CI): Adjusted for age and Baseline Cannabis use

A p≤0.005; B p≤0.01; C p≤0.05
Limitations and conclusions

- Self-report data
- Difficulty measuring extent of cannabis use
- How much vs. how it is used
- No data on strain (indicas vs. sativas, etc.)
  - See Vandrey et al. JAMA, 2015

- Generalizability
  - Only from select clinics in Michigan

- Conclusions:
  - Those using medical cannabis are older, relatively sick and have poor functioning
  - Medical cannabis patients are disconnected from larger health systems
  - Medical cannabis patients use large quantities of both cannabis and opioids
Treating chronic pain in patients with Substance Use Disorders
Clinical implications of co-occurring pain and SUDs

- Chronic pain is common in patients seeking SUD treatment
- Chronic pain is associated with a poorer course of post-treatment outcomes following SUD treatment (Larson et al. 2007).
  - In a large addictions treatment program, patients with persistent pain were more likely to drop out of treatment and were less likely to be abstinent at 1-year (Caldeiro et al. 2008).
- Need to improve treatment for pain among SUD patients
Methods

1. 130 patients recruited at the start of an episode of VA outpatient SUD treatment (IAC 09-047)
   - No inclusion/exclusion criteria related to SUDs
   - Required pain of at least moderate or greater
2. All participants received treatment as usual in the Ann Arbor VA outpatient SUD program (1-3 sessions per week, relapse-prevention and harm-reduction model; encouragement of self-help group attendance) as well as usual treatment from other treatment providers.

Ilgen, Bohnert, Chermack, Conran, Jannausch, Trafton, Blow. (2016) *Addiction*
Methods

- Participants were randomized to one of two 12-week groups:
  - CBT for pain and SUDs
  - Supportive Psychoeducation Control (SPC) — similar in structure to what has been used in other SUD studies (Fals-Stewart & Klostermann, 2004) w/ specific pain content
- Participants were followed at 3-, 6-, and 12-months with goal of examining impact of random assignment (CBT vs. SPC) on pain, functioning and substance use
  - 3-month (81.82%)
  - 6-month (85.61%)
  - 12-months (84.09%)
Pain level over 12-months

CBT -0.65 (0.29); p < 0.05
Pain-related functioning over 12-months

WHY MPI General Activity score

CBT 0.25 (0.11); p < 0.05
Alcohol use over 12-months

CBT -0.91 (0.35); p < 0.05
Drug use over 12-months

CBT -0.07 (0.31); NS
Recently completed a new study (R01 DA029587) to examine this same intervention in adults seen in a large residential SUD treatment program:

- Sample of 226 male and 226 female participants (3 more rounds of groups to go)
- Addition of behavioral measures of pain tolerance
Summary
Conclusions related to pain and SUDs

- Chronic pain and SUDs frequently co-occur and the presence of one condition complicates the treatment of the other.

- The Opioid Epidemic – increasing access to opioids is associated with increase in adverse outcomes
  - Improved policies are needed to limit risky opioid prescribing
  - Medical cannabis could decrease opioid-related problems
  - However, our early analyses of individual-level data do not support this. More work is needed to make this determination.

- Non-pharmacologic treatments have a role to play in addressing pain in those with SUDs
  - These strategies have the potential to improve pain and substance-related outcomes as well as reduce the likelihood of adverse events.
Clinical implications

- Ask about opioid misuse (items from the COMM):
  - “How often have you needed to take pain medications belonging to someone else?”
  - “How often have you had to take more of your medication than prescribed?”
  - “How often have you borrowed pain medication from someone else?”
  - “How often have you used your pain medication for symptoms other than for pain?”

- Ask about cannabis use:
  - What’s the “prescription”? 
  - What’s the major motivation for use?
  - Quantity/frequency
  - Route of administration
  - How would the patient know if s/he is getting into trouble?
  - Co-use with opioids, alcohol or nicotine
Thank You!

Please feel free to contact me:

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