The Opioid Crisis: Is There a Role for Medical Cannabis?

Mark S. Wallace, M.D.
Professor of Clinical Anesthesiology
University of California, San Diego
Oversupply of pain pills after surgery helps fuel opioid epidemic

How to stop the deadliest drug overdose crisis in American history

EDITORIAL: Opioid crisis takes on urgent tone

News From the Food and Drug Administration

PUBLIC HEALTH

Should Hospitals Be Punished For Post-Surgical Patients’ Opioid Addiction?

Unintended consequences: Inside the fallout of America’s crackdown on opioids
The US treats pain with opioids

- > 1 in 3 adults in US took an opioid in 2015  
  ≈ 50% non-cancer pain  ≈ 30% for post op pain  ≈ 20% cancer  
  National Institute on Drug Abuse 2017  

- US prescribed 70% of the world’s supply of opioids in 2014  
  - 99% of hydrocodone  
  - 51% of morphine  
  International Narcotics Control Board. Statistical information on narcotic drugs 2011  

- 4x higher than in Europe in 2015
Prescription Opioid Deaths Continue to Rise

National Overdose Deaths
Number of Deaths from Prescription Opioid Pain Relievers

Source: National Center for Health Statistics, CDC Wonder
How Healthy Are We?

- 1 person dies from a overdose in the US every 9 min \(^{1}\) National Center for Health Statistics; 2017

- 1 in 5 say they know someone addicted to opioids \(^{2}\) Federal Reserve Report May 2018

- 20% of the decline of males in the labor force due to opioid abuse \(^{3}\) Brookings Paper on Economic Activity 2017

- > 115 die in US daily from opioid overdoses \(^{4}\) NCHS Data Brief 2017

- > 50% prescription opioids are used by pts with mental health disorders \(^{5}\) J Am Board Fam Med. 2017

- ≈ 500 start heroin use each day and within 12 m ≈ 40% of new heroin users have become dependent on heroin \(^{6}\) JAMA Psychiatry 2018
Who is Dying

- Disproportionate numbers of overdose deaths associated with methadone and fentanyl
- Fatal overdose risk associated with co-prescription of opioids and benzodiazepines
- Risks associated with sleep-disordered breathing, reduced renal or hepatic function, older age, pregnancy, mental health comorbidities, and history of substance use disorder
- High risk of overdose at start of therapy and with increase
CDC Guidelines for Prescribing Opioids for Chronic Pain - 12 Recommendations

• Improve communication between providers and patients about risks/benefits and to improve safety and effectiveness

• Primarily targeted at Primary Care Physicians

• Not intended for patient who are in active cancer treatment, palliative care, or end-of-life care

• Not intended to dictate Standard of Care

Jama 315(15) 1625-1645
History of Medicinal Cannabis

- China, 1st century: rheumatic pain, constipation…
- India: sedative, anxiolytic, anticonvulsant, analgesic…
- 1839: Dr. William O’Shaughnessy
- U.S. Dispensatory 1845: analgesic in place of opium
- Late 19th/Early 20th Century:
  - migraine, neuralgia, dysmenorrhea, acute rheumatism, dental pain
  - multiple patent medicines
- Removed from pharmacopoeia in 1942
  - Against advice of the AMA
- 1996: California prop 215
History of Opioids

Opioids described favorably by ancient Sumerians and Egyptians (c 3400-1300 BC)

Greek descriptions (c 460 BC) of harmful effects of opioids

Galen recommended opium as a cure for many conditions (c AD 150-210)

Opium introduced to China by Arab traders (c AD 400)

Opium disappeared from European history record for 200 years (c AD 1300)

Late 17th–18th centuries: reports of opium abuse described

Sertürner (1803) synthesized morphine

Wright synthesized heroin (1874)
History of Opioids

- Early 20th century: Restriction of opioids
  - morphine addiction grows
  - “morphine maintenance” clinics proliferate
  - harsh legislation severely limits opioid availability

- 1960s–1990s: Rejustification of opioid use
  - growth of hospice and palliative care movements
  - growth of patients’ rights movement
  - JCAHO guidelines
  - controlled clinical trials show opioid efficacy for acute and cancer pain
  - data suggest addiction potential possibly overstated
  - DEA, FDA, Federation of State Medical Boards, APS, AAPM, ASAM, ACR, AGS
    - all issue guidelines supporting appropriate use of opioids for chronic pain

- 1990s: THE OPIOID CRISIS BEGINS
Medical Marijuana Controversy

**PRO**
- Leaf contains many active constituents making it more efficacious than single component extract
- No lethal dose
  - >19,000 deaths/year from prescription opioids
- Low dependency
- Millennia support safety and efficacy

**CON**
- Legalization will lead to more recreational use
- Will never meet FDA criteria for approval
- Gateway to drug abuse
- Colorado seeing increase discharges from marijuana toxicity
  - but no deaths
Map of U.S. Marijuana Legalization

- Medical:
  - 29 states & DC
- Recreational & Medical:
  - 9 states & DC
- CBD Only:
  - 17 states

As of May 2018
Medicinal Cannabis: Access

- Varies by State
  - Cultivation
  - Possession
  - ID Cards
  - Diagnosis restrictions
  - Dispensaries
    - www.weedmaps.com
    - www.medicalmarijuana.procon.org
Medicinal Cannabis: Cannabinoid Pharmaceuticals

**THC** schedule 1

**Dronabinol** (Marinol) schedule III
FDA approved for: HIV wasting & chemo nausea

**Nabilone** (Cesamet) schedule II
FDA approved for: chemo nausea

**Nabiximols** (Sativex) Not FDA approved in US; Canada & Europe: Cancer pain, spasticity
CANNABINOIDS

Two cannabinoid (CB) receptors: CB1/CB2

G protein coupled superfamily 7 TM
- positively to potassium channels and
gen active protein kinase (MAPK)
- negatively to N-type and P/Q-type calcium
  channels and adenylate cyclase
  (responsible for THC psychoactive effects)
CANNABINOID TARGETS

Peripheral Cells: monocytes, B/T and mast cells

CB2-r:
↓ Inflammatory cell mediator release
↓ Plasma extravasation
↓ Sensitization of afferent terminals

Peripheral terminal of Primary afferent.

CB1-r:
↓ Terminal excitability
↓ Release of pro-inflammatory terminal peptides

CB-r agonists: reduction of elevated terminal excitability otherwise induced by local injury and inflammation.
CANNABINOID TARGETS
Spinal Dorsal Horn

CB1-r: (intrathecal)

*Presynaptic* - Terminals of small primary afferents (peptidergic and non peptidergic)..partial colocation with TRPV-1-r
Agonist: ↓N/P/Q-VSCC →↓ neurotransmitter release

*Post synaptic* - neurons: (mRNA): Lam I-V, X
Agonist: ↑K Ch → hyperpolarization →↓ excitability

CB1-r/ CB2-r:
*Non neuronal cells* (??)

CB1 agonists: reduction of afferent evoked excitation of dorsal horn nociceptive neurons.
CANNABINOID TARGETS

Supraspinal Sites

CB1-r (microinjection)
Basolateral Amygdala
Periaqueductal gray
Rostroventral Medulla

Local effects upon nociceptive processing

Activation of bulbospinal pathways…regulating dorsal horn excitability

CB1 agonists: reduction of afferent evoked excitation of dorsal horn nociceptive neurons.
Cannabinoid Refers to a Variety of Compounds

- Endocannabinoids
  - Endogenous cannabinoids
- Phytocannabinoids
  - Derived from cannabis plants
- Synthetic
Two Families of Endocannabinoids

Anandamide
- Amide of ethanolamine and arachidonic acid
- Made by hydrolysis of N-arachidonoyl phosphatidyl ethanolamine (NAPE) by phospholipase D
- Low efficacy agonist (similar to $\Delta^9$THC)
- Degraded by fatty acid amino hydrolase (FAAH)

2-arachidonyl glycerol (2-AG)
- Far more abundant than anandamide
- Made by hydrolysis of phosphatidylinositol by phospholipase C and diacylglycerol lipase
- High efficacy agonist
- Degraded by monoacylglycerol lipase (MAG)

Both are “made on demand” and enhanced by neural activity
THE ENDOCANNABINOID SYSTEM

Implicated in processes such as pain, perception, mood, memory and reward.

To provide that we:

EAT  SLEEP  RELAX  FORGET  PROTECT

Medicinal Cannabis: Pharmacology

• Cannabis contains > 400 compounds; > 80 are cannabinoids

• Delta-9-tetrahydrocannabinol (THC) - main psychoactive cannabinoid
  – Highly lipid soluble
  – High affinity for CB1 & CB2
  – Analog of the endogenous cannabinoid anandamide

• Cannabidiol (CBD) – non-psychoactive cannabinoid
  – Low affinity for CB1 & CB2 – possibly agonist/antagonist
  – Activates TRPV-1 – inhibitor of cyclooxygenase
  – Has anticonvulsant, muscle relaxant, sedative, and anti-inflammatory activity
  – May attenuate the psychoactive properties of THC
Medicinal Cannabis: Evidence for Pain

- Pre-Modern use for pain
- Experimental Pain
- Modern studies of pain
  - Limited & small studies
  - Best evidence: neuropathic pain
  - Wide variation in study product
Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

Mary E. Lynch and Fiona Campbell

Department of Anesthesia, Psychiatry, Dalhousie University, Halifax, Canada, and Department of Anesthesia and Pain Medicine, Hospital for Sick Children, University of Toronto, Toronto, Canada

Correspondence
Of Mary E. Lynch, M.D., FRCP, Pain Management Unit, Queen Elizabeth II Health Sciences Centre, 4th Floor Divisional Centre, Room 4060, Halifax, Nova Scotia, B3H 1X1, Canada.
Tel: +1 902 472 4631
Fax: +1 902 472 4126
E-mail: maryelynch@telus.net

Keywords: cannabinoids, chronic non-cancer pain, neuropathic pain, systematic review

Received: 22 December 2010
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Accepted Article: 7 March 2011

Fifteen of the eighteen trials that met the inclusion criteria demonstrated a significant analgesic effect of cannabinoid as compared with placebo and several reported significant improvements in sleep. There were no serious adverse effects. Adverse effects most commonly reported were generally well tolerated, mild to moderate in severity and led to withdrawal from the studies in only a few cases.

Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis.
Health Effects of Cannabis and Cannabinoids: Report of the National Academies of Sciences, Engineering and Medicine

- Therapeutic Effects
- Cancer incidence
- Cardiometabolic risk
- Respiratory disease
- Immune function
- Injury and death

Levels of Evidence:

Conclusive  Limited
Substantial   No or Inconclusive
Moderate
Health Effects of Cannabis and Cannabinoids: Report of the National Academies of Sciences, Engineering and Medicine

- Therapeutic Effects
  - Cancer incidence
  - Cardiometabolic risk
  - Respiratory disease
  - Immune function
  - Injury and death

- Prenatal, perinatal, postnatal outcomes
- Psychosocial outcomes
- Mental Health
- Problem cannabis use
- Cannabis use and abuse of other substance

Levels of Evidence:
- Conclusive
- Limited
- Substantial
- No or Inconclusive
- Moderate

BEST EVIDENCE
Medicinal Cannabis: AEs & Safety

COMPASS Study

• 1 yr. prospective cohort; 531 chronic pain patients
• No difference serious AEs
• Cannabis grp.: > non-serious AEs
  – Nervous system; psychiatric; respiratory
• No difference: neurocognitive, heme, liver, renal, endocrine function
• Cannabis > Controls:
  – Pain intensity improvement
  – Symptom distress & mood disturbance

Cannabinoid/Opioid System Interactions

• Animal studies indicate a contribution of the opioid system in cannabinoid reward, reinforcement and dependence
  – Opioid agonists facilitate while antagonist reduce self administration of cannabinoids
  – Naloxone induces cannabinoid withdrawal while co-administration prevents dependence
  – Opioids attenuate cannabinoid withdrawal

• Opioid modulation in humans less clear

Cooper ZV, Haney M. Int Rev Psychiatry, 2009, 104-112
Cannabis: Abuse Potential

• Although cannabis abuse is prevalent, animal studies show that cannabinoids do not seem to be as robust as other agents (heroin, cocaine, nicotine)

Cooper ZV, Haney M. Int Rev Psychiatry, 2009, 104-112
Problematic Opioid vs Cannabis Use: Pain Patients

Cannabis Tolerance

• With chronic cannabis use, tolerance develops to the physiological (i.e. cardiovascular) and subjective (i.e. highness) effects.

Cannabis: Dependence and Withdrawal

- Abrupt termination in habitual users results in withdrawal symptoms similar to opioids
- Dependent on the dose of THC consumed
  - Less likely to occur or symptoms less with lower dose consumption

EFFECT OF MEDICAL CANNABIS LAWS ON OPIOID USE: THE GOOD AND THE BAD
THE GOOD
Population Studies are Emerging Suggesting That Medical Marijuana Patients are Substituting Marijuana for Opioids

Lucas, Pyschoactive Drugs, 2012
Lucas Addict Res Theory, 2013
Lucas, Int J Drug Policy, 2017
Reiman, Harm Reduct, 2009
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

Table. Association Between Medical Cannabis Laws and State-Level Opioid Analgesic Overdose Mortality Rates in the United States, 1999-2010

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a Law</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary Analysis</td>
</tr>
<tr>
<td></td>
<td>Estimate (95% CI)</td>
</tr>
<tr>
<td>Medical cannabis law</td>
<td>-24.8 (-37.5 to -9.5)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prescription drug monitoring program</td>
<td>3.7 (-12.7 to 23.3)</td>
</tr>
<tr>
<td>Law requiring or allowing pharmacists to request patient identification</td>
<td>5.0 (-10.4 to 23.1)</td>
</tr>
<tr>
<td>Increased state oversight of pain management clinics</td>
<td>-7.6 (-19.1 to 5.6)</td>
</tr>
<tr>
<td>Annual state unemployment rate&lt;sup&gt;g&lt;/sup&gt;</td>
<td>4.4 (-0.3 to 9.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup> All models adjusted for state and year (fixed effects).
<sup>b</sup> $R^2 = 0.876$.
<sup>c</sup> All intentional (suicide) overdose deaths were excluded from the dependent variable; opioid analgesic overdose mortality is therefore deaths that are unintentional or of undetermined intent. All covariates were the same as in the primary analysis; $R^2 = 0.873$.
<sup>d</sup> Findings include all heroin overdose deaths, even if no opioid analgesic was involved. All covariates were the same as in the primary analysis. $R^2 = 0.842$.
<sup>e</sup> $P \leq .05$.
<sup>f</sup> $P \leq .001$.
<sup>g</sup> An association was calculated for a 1-percentage-point increase in the state unemployment rate.
Medical Marijuana Policies and Hospitalization Related to Marijuana and Opioids

- Hospital discharges 1997-2014
- Medical Marijuana Policies associated with:
  - No change in Marijuana dependence or abuse discharges
  - 23% reduction in Opioid dependence or abuse discharges
  - 13% reduction in Opioid pain reliever overdose discharges

- Shi, Y. Drug and Alcohol Dependence, 2017
Association Between Prescribing Patterns for Opioids in Medicare Part D and the Implementation of State MCLs

- Doses of opioids filled in Medicare D from 2010–2015
- Average of 23.08 million daily doses of any opioid dispensed/year across states
- Multiple regression analysis found fewer daily doses in states with MCLs
  - Active dispensaries – 3.742 million reduction
  - Home cultivation – 1.792 million reduction
- Largest effect seen on hydrocodone

JAMA Int Med, 2018
Cannabis Use Associated with Decreased Opiate Use

• A retrospective cross-sectional survey of patients with chronic pain
  – 64% decreased opioid use
  – Decreased side effects of medications
  – Improved quality of life

Recreational Marijuana Legalization and Prescription Opioids in Medicaid Patients

- Prescription drug utilization 2010-2017
- 3 population-adjusted variables: # opioid prescriptions, total MME, related Medicaid spending
- Legalization associated with Schedule III but not II opioid reduction:
  - Reduction in # prescriptions – 32%
  - MME – 30%
  - Spending on schedule II opioids – 31%

Shi, publication pending, 2018
Cannabis and Driving

- States with Medical Marijuana Laws have fewer traffic fatalities
  - Fatality Analysis Reporting System 1985-2014
    - Age 15-24 – 11% reduction
    - Age 25-44 – 12% reduction
    - Age 45 and older – no significant change
  - State specific immediate reductions
    - California – 16%
    - New Mexico – 17.5%
    - However, there has been a gradual increase since laws passed

THE BAD
Cannabis Use and Risk of Prescription Opioid Use Disorder

- Cannabis use, increase nonmedical prescription opioid use and opioid use disorder
- Adults with pain and cannabis use, increase nonmedical opioid use

Olfson, Am J Psychiatry, 2018
Effect of Cannabis Use in Chronic Pain Patients Prescribed Opioids

- 4 year prospective, national, observational cohort study in chronic pain patients on opioids
- 1514 included in the study
  - 24 % reported using cannabis
  - Compared to no cannabis used:
    - > pain severity score
    - > pain interference score
    - > generalized anxiety disorder severity score
  - No evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation

Campbell, Lancet Public Health, 2018
Cannabis: Conditioned Placed Preference vs. Aversion

- High dose THC produces CPA
- Lower doses of THC produces CPP
- Human cannabis smokers also report opposing effects

Braida D, Pozzi M, Cavallini R, Sala M
Neuroscience. 2001; 104(4):923-6
Cheer JF, Kendall DA, Marsden CA
Psychopharmacology (Berl). 2000 Jul;
CBD
15 mg: 'alertness'
160 mg: increased sleep duration
3-400 mg: anxiolytic
> 400 mg: antipsychotic

THC
2-5 mg: anxiolytic/analgesic
10-15 mg: paranoia
20-25 mg: psychosis, sedation, hyperalgesic

Bi-phasic effects

VAMS Anxiety post-stress

Placebo Clonazepam

CBD
100 300 900

3-400 mg: anxiolytic
> 400 mg: antipsychotic
Therapeutic window of pain relief occurs between 16-31 ng/ml plasma level of THC.
CBD could reduce the incidence of psychoactive effects induced by THC.
Other Cannabis Compounds with Medicinal Properties

- **Myrcene**
  - Analgesic effect
  - Blocked by naloxone or yohimbine
  - Anti-inflammatory effect
    - Through PGE2 inhibition
- **Linalool**
  - Possible reduction of stress
- **Limonene**
  - Adenosine agonist
- **Caryophyllene**
  - CB2 agonist
  - Anti-inflammatory
  - Beta-caryophyllene is an FDA approved dietary supplement
- **Humulene**
  - Anti-inflammatory
    - Effects similar to dexamethasone
  - Inhibits TNFα and IL1B
Clinical Pharmacology of Marijuana: Route-Dependent Pharmacokinetics
Cannabinoids and Sleep

- Not much known about the effects on sleep
- THC and CBD biphasic and different doses affect sleep differently
- THC alone had no effect on sleep quality
- Low dose CBD is stimulating and reduced stage 3 and wakefulness
- High dose CBD is sedating
- No studies on combination therapy

Cannabis Use and Driving

• Very little research on Driving
• Appears to have much less affect on motor skills than alcohol
• However, combination of alcohol and cannabis can result in severe impairment
• General rule
  – Ingestion – no driving for 8 hours
  – Trans mucosal – no driving for 4 hours
  – Inhalation – no driving for 2 hours
Still Unclear and Unanswered Questions

- Should they be as strict as opioids?
- Role of UDT
- Role of Patient Agreements
- Concurrent use of opioids or wean first
- Dosing
UCSD Pain Clinic Approach to Medical Marijuana

- Failure of conservative therapies
  - Consider before chronic opioids
- Provide authorization via the DPH application
- Dosing consultation
- If using chronic opioids, start wean first
  - Consider introducing cannabis during wean for compliant patients
- Follow up: document type and dose if known
- Consider UDT
THE END

IT'S OLD, NEVER RUNS AND IT COSTS ME A FORTUNE. BUT, I STILL HAVE FAITH IN IT.