Medicinal Cannabis for Pain: Texas Pain Society

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Disclosures

- Nothing to disclose

Medicinal Cannabis & Pain

- History of cannabis as medicine
- Safety
- Evidence for pain

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 pai
  - multiple patent medicines
- Removed from pharmacopoeia in 1942
  - Against advice of the AMA
- 1996: California prop 215

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: 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

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

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

	Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a Law		
	Primary Analysis	Secondary Analyses	
Independent Variable[a]	Estimate (95% CI)[b]	Estimate (95% CI)[c]	Estimate (95% CI)[d]
Medical cannabis law	−24.8 (−37.5 to −9.5)[e]	−31.0 (−42.2 to −17.6)[f]	−23.1 (−37.1 to −5.9)[e]
Prescription drug monitoring program	3.7 (−12.7 to 23.3)	3.5 (−13.4 to 23.7)	7.7 (−11.0 to 30.3)
Law requiring or allowing pharmacists to request patient identification	5.0 (−10.4 to 23.1)	4.1 (−11.4 to 22.5)	2.3 (−15.4 to 23.7)
Increased state oversight of pain management clinics	−7.6 (−19.1 to 5.6)	−11.7 (−20.7 to −1.7)[e]	−3.9 (−21.7 to 18.0)
Annual state unemployment rate[g]	4.4 (−0.3 to 9.3)	5.2 (0.1 to 10.6)[e]	2.5 (−2.3 to 7.5)

[a] All models adjusted for state and year (fixed effects).

[b] R^2 = 0.876.

[c] 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.

[d] 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.

[e] $P \leq .05$.

[f] $P \leq .001$.

[g] An association was calculated for a 1-percentage-point increase in the state unemployment rate.

JAMA Internal Medicine | Original Investigation | HEALTH CARE POLICY AND LAW

Association Between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population

Ashley C. Bradford, BA; W. David Bradford, PhD; Amanda Abraham, PhD; Grace Bagwell Adams, PhD

JAMA Internal Medicine | Original Investigation | HEALTH CARE POLICY AND LAW

Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees

Hefei Wen, PhD; Jason M. Hockenberry, PhD

Medicare Population:

- 8.5% reduction in total daily dose opioids Rx (not statistically significant)
- 14.1% reduction in total daily dose opioids for states with dispensaries (significant)

Medicaid Population:

- 5.88% lower rate of opioid prescribing

Medicinal Cannabis: Safety Issues

- No Federal regulation: production, purity, potency
  - State oversight varies
  - Greater oversight/regulation in recreational states
- No way to clearly specify a dose
- Abuse & Dependence
  - Abuse potential lower than opioids
  - Regular/heavy users may experience withdrawal
- No clear lethal dose

Medicinal Cannabis: Evidence for Pain

- Modern studies of pain: limited & small
- Best evidence: neuropathic pain
- Wide variation in study product

Cannabis & Pain: Meta-Analyses

- Lynch et al (2011 Br J Clin Pharmacol)
  - 18 RCT in chronic non-cancer pain
  - Mixed cannabis types and delivery routes
  - Cannabinoids are safe and modestly effective for neuropathic pain
- Andreae et al (2015 *J Pain*)
  - Inhaled cannabis for neuropathic pain
  - 5 RCT studies included
  - Odds ratio of 30% reduction 3.2 with NNT of 5.5
- Stockings et al, (2018 epub ahead of print *Pain*)
  - 104 RCT and observational studies, mixed CNCP (half were neuropathic pain)
  - Mixed cannabis types and delivery routes
  - Evidence of 30% reduction in pain vs placebo; no evidence of 50% reduction
  - NNTB 29
  - NNTH 6

RCTs of Smoked Cannabis in Pain

N=	Indication	Duration/type	Outcome
50	HIV neuropathy	5 days/DB	Decreased pain and hyperalgesia (Abrams, 2007)
16	Diabetic Peripheral Neuropathy	Single dose/DB/Crossover	Decreased pain (Wallace, 2015)
38	Neuropathic pain	Single dose/DBC	Decreased pain w/ highest dose, but significant psychoactive effects (Wilsey, 2008)
34	HIV neuropathy	5 days/DB	Improved pain vs placebo, (Ellis, 2009)
21	Chronic pain on opioids	5 days/DB	27% decrease in pain (Abrams, 117)
42	Spinal cord injury	Single dose/crossover	Decreased pain, no difference between low and high dose (Wilsey, 2016)

RCTs of Synthetic Cannabinoids in Pain

N=	Agent	Indication	Duration/type	Outcome
21	Ajulemic acid	Neuropathic pain	7 day crossover	Decreased pain (Karst, 2003)
24	Dronabinol	Neuropathic pain in MS	15-21 days/DBC	Median numerical pain and relief improved (Svendsen, 2004)
40	Dronabinol	Postop pain	Single dose/DB	No Benefit (Buggy, 2003)
30	Dronabinol	Chronic pain	3 doses, 1 day/DB	Total pain relief improved with 10 and 20 mg. AEs prominent, (Narang, 2008)
31	Nabilone	Fibromyalgia	2 weeks/DBC	No effect on pain; sleep improved (Ware, 2010)
96	Nabilone	Neuropathic pain	14 weeks/DBC vs dihydrocodeine	DHC more effective with fewer AE (Frank, 2008)

RCTs of Cannabis-Based Medicines in Neuropathic Pain

N=	Agent	Indication	Duration/Type	Outcomes
20	Nabixmols	Neurogenic pain	2 week crossover	Decreased pain, (Wade, 2004)
117	Nabixmols	Spinal cord injury pain	10 days	No effect on pain (unpublished)
48	Nabixmols vs THC	Brachial Plexus Avulsion	6 wks in 3 two-week arms	Decreased pain, (Berman, 133)
66	Nabixmols	Central neuropathic pain of MS	5 weeks	Decreased pain, (Rog, 2005)
125	Nabixmols	Peripheral neuropathic pain	5 weeks	Decreased pain and allodynia, (Nurmikko, 135)
65	Cannador	Post Herpetic neuralgia	4 weeks	No benefit (Ernst, 2005)
419	Cannador	Pain in MS	15 weeks	Decr spasm-related pain, No decr in Spasms (Zajicek, 2003)

RCTs of Cannabis-Based Medicines in Cancer Pain

N=	Agent	Indication	Duration/type	Outcome
36	Oral THC	Cancer Pain	Single dose; vs codeine	Decreased pain similar to codeine; high dose cannabis >AE than codeine, (Noyes, 1975)
117	Nabixmols	Cancer Pain	2 weeks	Decreased pain, (Johnson, 138)
360	Nabixmols	Cancer Pain	5 weeks/DB	Decreased pain in low and middle dose, (Portenoy, 2012)

Conclusions

- Cannabis has a very long history in medicine
- Compared to opioids, cannabinoids have a good safety profile
- Evidence for pain exists but remains limited
- Federal legal status & limited/no regulation remains a major challenge