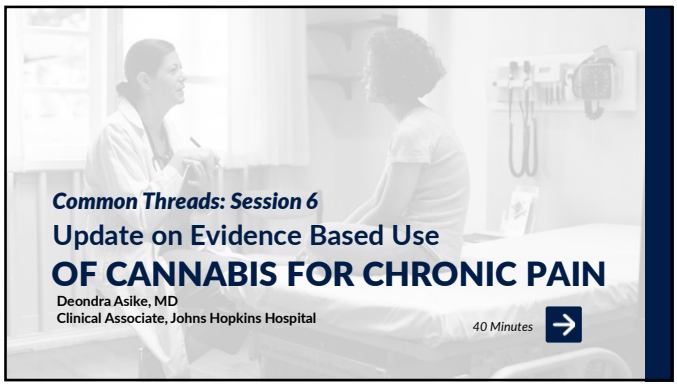


Common Threads: Session 6

Update on Evidence Based Use
OF CANNABIS FOR CHRONIC PAIN

Deondra Asike, MD
Clinical Associate, Johns Hopkins Hospital

40 Minutes

Disclosures

No financial disclosures.
The views and opinions expressed herein are solely my own.

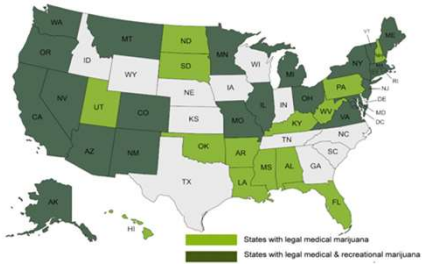
Audience Response

Do you practice in a state with a medical cannabis program?

Yes | No | I don't know

Marijuana Legality in the United States

As of December 2023



SOURCE: https://medicalmarijuana.procon.org/legal-medical-marijuana-states-and-dc/

Experiences With Chronic Pain

- **51.6 million**
  persons experienced chronic pain[1]
- **17.1 million**
  with substantial restriction to daily activities[1]
- **1/3**
  of the 1661 adults surveyed self-reported using cannabis for chronic pain[2]

The New York Times

January 12, 2024

Federal Scientists Recommend Easing Restrictions on Marijuana

In newly disclosed documents, federal researchers find that cannabis may have medical uses and is less likely to cause harm than drugs like heroin.

"The largest evidence base for effectiveness exists for marijuana use within the pain indication (in particular, neuropathic pain)...."[3]

"Additionally, no safety concerns were identified in our review that indicate that medical use of marijuana poses unacceptably high safety risks for the indications where there is some credible scientific evidence supporting its therapeutic use."

- Department of Health and Human Services-

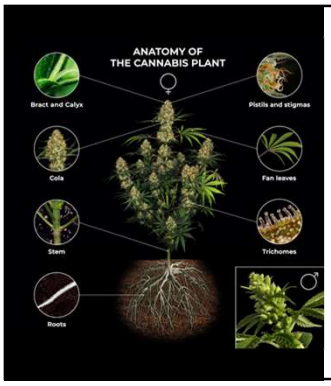
Session Learning Objectives

01 List the positive and negative effects of cannabinoids and modulators of the endocannabinoid system.

02 Discuss the evidence for efficacy and safety of cannabinoids as pain treatments.

03 Discuss the challenges to cannabis research.

04 List additional sources of "evidence" to help guide clinical practice.



Cannabis

- Whole plant, parts or plant material
- PhytoCannabinoids (e.g., THC, CBD)
- Non-Cannabinoids (e.g., terpenes and flavonoids)

Important Terms and Definitions

Cannabinoids

- Molecules with activity at cannabinoid receptors
  - Phytocannabinoids (e.g., THC, CBD)
  - Endocannabinoids (AEA, 2-AG)
  - Synthetic (CBMs or drugs of abuse)

Cannabis-Based Medications (CBMs)

- Approved for medical use
  - synthetic (e.g., Dronabinol, Nabilone)
  - plant-derived (e.g., Epidiolex, Nabiximols)

Cannabis Products

- Dried flower, concentrates, tinctures, topicals, edibles

Cannabinoids, the endocannabinoid system, and pain: a review of preclinical studies


PAIN
NARRATIVE REVIEW
Cannabinoids, the endocannabinoid system, and pain: a review of preclinical studies

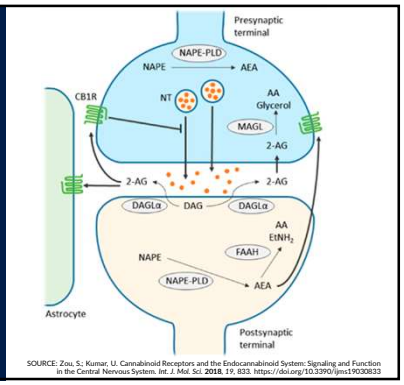
Narrative review informed by systematic review and meta-analysis of 347 published preclinical studies investigating pain-related efficacy and pain-related effects of cannabis, cannabinoids, and endocannabinoid system modulators

Endocannabinoids
(2-AG and AEA)

Cannabinoid Receptors
(CB1R and CB2R)

Endocannabinoid Synthesis
(NAPE-PLD and DAGL)

Endocannabinoid Catabolism
(MAGL and FAAH)



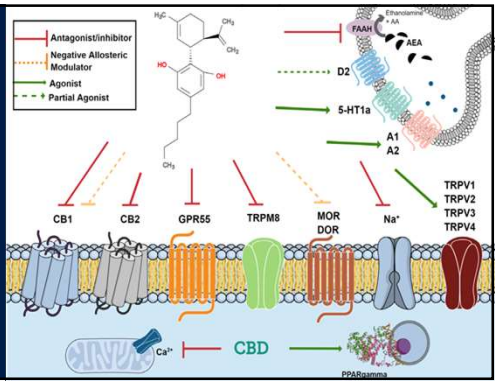
SOURCE: Zou, S.; Kumar, U. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. *Int. J. Mol. Sci.* **2018**, *19*, 833. https://doi.org/10.3390/ijms19030833

THC & CBD

THC:
Non-selective ligand and agonist of CB1R and CB2R

CBD:
Various targets

Cannabidiol (CBD)



Antinociceptive Efficacy

"…substantial evidence from animal model experiments supports the hypothesis of cannabinoid-induced analgesia in inflammatory and neuropathy conditions."[4]

Inflammatory Pain Models
CB1R Agonists
CB2R Agonists
PEA
THC

Neuropathic Pain Models
CBD
FAAH inhibitors
CB1R Agonists
CB2R Agonists
PEA
THC

Pain-Related Effects

- Synergism with Non-opioids
- Synergism with Opioids
- Motor Impairment
- Tolerance
- Physical Dependence
- Reward/Reinforcing Effects

Antinociceptive Synergy with Non-Opioids

- THC
- CBD
- Anandamide
- MGL Inhibitor

Non-Opioids

- Gabapentin
- Tylenol
- COX-Inhibitors (selective & non-selective)

Antinociceptive Synergy with Opioids

- CB1 & CB2 receptor agonists
- Endocannabinoid Deactivation Inhibitors (MGL & FAAH Inhibitors)

	Analgesia	Motor Impairment	Tolerance To Analgesia	Tolerance To Motor Impairment	Physical Dependence	Reinforcing Effects
CB1 receptor agonist (central)	YES	YES	YES (esp. high doses)	YES	YES	YES
CB1 receptor agonist (peripheral)	YES	NO	NO	NO	NO	NO
CB2 receptor agonist	YES	NO	NO	NO	NO	NO
Nonselective CB1, CB2 receptor agonist	YES	YES	YES	YES	YES	YES
Low Dose MGL inhibitor	YES	NO	NO	NO	?	NO
High Dose MGL inhibitor	YES	YES	YES	?	YES	NO
FAAH inhibitor	YES	NO	NO	NO	NO	?

Knowledge Check

Which molecular targets of cannabinoid-mediated pain transmission demonstrate properties of analgesia, motor impairment, tolerance, and reward effects?

A. Peripheral CB1 Receptor Agonists only

B. Central CB1 Receptor Agonists only

C. Nonselective CB1/CB2 Receptor Agonists only

D. Both Central CB1 Receptor Agonists and Nonselective CB1/CB2 Receptor Agonists

Knowledge Check

Which molecular targets of cannabinoid-mediated pain transmission demonstrate properties of analgesia, motor impairment, tolerance, and reward effects?

A. Peripheral CB1 Receptor Agonists ✗

B. Central CB1 Receptor Agonists only ✗

C. Nonselective CB1/CB2 Receptor Agonists only ✗

D. Both Central CB1 Receptor Agonists and Nonselective CB1/CB2 Receptor Agonists ✓

Correct Answer: D

According to the findings published in *Cannabinoids, the endocannabinoid system, and pain: a review of preclinical studies*[4],

"Both nonselective CB1/CB2 receptor agonists and central CB1 receptor agonists demonstrate antinociceptive, motor impairment, tolerance, physical dependence and negative reinforcing effects."


PAIN

NARRATIVE REVIEW

Cannabinoids, the endocannabinoid system, and pain: a review of preclinical studies

Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials

- Systematic Review of RCTs
- **36 out of 165** full texts met inclusion criteria
- **1° Outcome:** 30% and 50% pain intensity reduction
- **2° Outcome:** Adverse Events, Sleep Duration/Quality, Function (Physical & Emotional)
- Ratings for Risk of Bias and Quality of Evidence

Efficacy by Treatment Duration

< 1 week	> 1 week
Beneficial effect: • Cannabis *No beneficial effect:* • CBMs	*Small benefit:* • Nabiximols *No benefit:* • THC • PEA • FAAH Inhibitors

Efficacy by Pain Condition Type

Small Benefit

- Neuropathic pain

No Benefit

- Acute pain
- Cancer-related pain
- MS
- Pelvic pain
- Carpal tunnel syndrome
- Low back pain

Adverse Events & Serious Adverse Events

Adverse Events:

No difference:
- PEA
- FAAH Inhibitors
- CBR Agonists

Higher:
- Nabiximols
- THC
- Cannabis

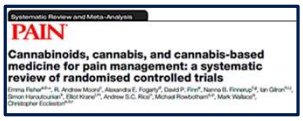
Serious Adverse Events:

No difference:
- Nabiximols
- THC
- Cannabis
- PEA
- FAAH Inhibitors

Other Secondary Outcomes:

- Improved **physical function**: Nabiximols (4 studies)
- Improved **sleep quality**: Nabiximols (13 studies)

Study Conclusion


Systematic Review and Meta-Analysis

PAIN

Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials

"The evidence neither supports nor refutes claims of efficacy and safety for cannabinoids, cannabis, or CBM in the management of pain."[5]

Knowledge Check

According to the systematic review by Fisher et al, which treatment provided a small analgesic benefit, improved function and improved sleep quality?

A THC

B PEA

C Nabiximols

D FAAH Inhibitors

Knowledge Check

According to the systematic review by Fisher et al, which treatment provided a small analgesic benefit, improved function, and sleep quality?

A THC ✗

B PEA ✗

C Nabiximols ✓

D FAAH Inhibitors ✗

Correct Answer: C

According to the findings published in: *"Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials"*[5], **improved physical function, improved sleep, and small analgesic benefit was reported with nabiximols.**

Thoughtfully Integrating Cannabis Products into Chronic Pain Treatment

Challenges to Translational Research

- Biological Differences
- Legal restrictions
- Cannabinoid isolation vs Whole-plant formulations
- Non-comparable routes of administration

Additional Considerations for Pain Research

ANIMAL STUDIES	HUMAN STUDIES
• Genetically identical	• Heterogeneous
• Male predominance	• Female predominance
• Young/healthy	• Older/co-morbidities
• Pain of short duration	• Pain of several months/years
• Evoked Limb Withdrawal	• Pain Intensity Rating

Where else can we turn for evidence?

Expanding the Definition of "Evidence"

Observational Studies:

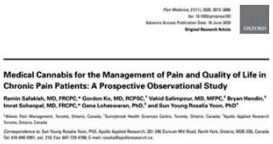
Pros:

- Larger sample size
- Reflects actual use patterns
- Representative of cannabis products sold in dispensaries

Cons:

- Biases (e.g., recall, selection)
- Lack of control group
- Relies on subjective measures

Medical Cannabis for the Management of Pain and Quality of Life in Chronic Pain Patients: A Prospective Observational Study


Medical Cannabis for the Management of Pain and Quality of Life in Chronic Pain Patients: A Prospective Observational Study

A longitudinal, prospective, observational study evaluating effects of plant-based medical cannabis in chronic pain patients over 12 months

Brief Pain Inventory

- Pain Intensity and Pain Interference

12-Item Short Form Survey (SF-12)

- Quality of Life
- Adverse Symptoms
- Daily Opioid Medication Dose
- Key Time points (B, M1, M3, M6, M12)

Medical Cannabis for the Management of Pain and Quality of Life in Chronic Pain Patients: A Prospective Observational Study

Table 3. *Measures of pain interference and pain severity as per the Brief Pain Inventory*

	BPI-Interference		BPI-Severity	
	Mean + SD	95% CI, P Value	Mean + SD	95% CI, P Value
Baseline (N=706)	6.23 + 1.63		5 .58 + 1.53	
Month 1 (N=584)	4.55 + 2.39*	0.48 to 2.88, 0.003	4.27 + 1.90*	0.47 to 2.14, 0.001
Month 3 (N=230)	4.08 + 2.97*	0.34 to 3.96, 0.013	3.89 + 2.17*	0.55 to 2.83, 0.001
Month 6 (N=105)	4.21 + 2.64*	0.45 to 3.58, 0.006	3.99 + 2.18*	0.30 to 2.87, 0.009
Month 12 (N=43)	3.54 + 2.84*	0.92 to 4.46, 0.001	3.49 + 2.17*	0.90 to 3.27, <0.001

Treatment with medical cannabis was found to be associated with significant changes in Brief Pain Inventory measures of pain interference ($F(4, 84)=8.99$, $P < 0.0005$, partial $12 =0.30$) and pain severity ($F(4, 84)=9.98$, $P < 0.0005$, partial $12 =0.32$).
BPI = Brief Pain Inventory; CI = confidence interval.
* *Denotes statistical significance in relation to baseline.*

Medical Cannabis for the Management of Pain and Quality of Life in Chronic Pain Patients: A Prospective Observational Study

Table 4. *Physical and mental health-related measures of quality of life as per the Short Form Health Survey*

	Mean + SD	Median	Sum of Ranks	Mean of Ranks	Test Statistics
Physical Composite Summary score					
Baseline (N=509)	31.21 + 8.09	30.18	911	2	Q (observed value)= 18
Month 1 (N=435)	32.99 ‡ 9.90	31.10	992	2	Q (critical value) = 9
Month 3 (N= 148)	34.05 + 9.42	31.80	993	7	DF = 4
Month 6 (N=69)	34.44 + 10.79	31.71	986	14	P < 0.05
Month 12 (N=31)	33.12 + 11.12	31.26	977	32	

Treatment with medical cannabis was found to be associated with significant changes in the Physical and Mental Health domains of the SF-12 over the course of the 12-month observation period.
DE = degrees of freedom; MCS = Mental Composite Summary; PCS = Physical Composite Summary; SF-12 = Short Form Health Survey.

Medical Cannabis for the Management of Pain and Quality of Life in Chronic Pain Patients: A Prospective Observational Study

Table 4. *Physical and mental health-related measures of quality of life as per the Short Form Health Survey*

	Mean ± SD	Median	Sum of Ranks	Mean of Ranks	Test Statistics
Mental Composite Summary score					
Baseline (N=509)	42.83 ± 11.53	41.59	915	2	Q (observed value)= 17
Month 1 (N=435)	46.55 ± 11.39	48.12	1,006	2	Q (critical value) =9
Month 3 (N= 148)	47.26 ± 11.23	48.40	989	7	DF = 4
Month 6 (N=69)	45.36 ± 11.74	45.92	973	14	P < 0.05
Month 12 (N=31)	51.05 ‡ 9.42	50.09	976	31	

Treatment with medical cannabis was found to be associated with significant changes in the Physical and Mental Health domains of the SF-12 over the course of the 12-month observation period.
DE = degrees of freedom; MCS = Mental Composite Summary; PCS = Physical Composite Summary; SF-12 = Short Form Health Survey.

Summary of Findings

- Sustained improvements in pain severity and pain interference *(1 month and beyond)*
- Positive improvements in measures of health-related quality of life *(3 months and beyond)*
- No serious adverse effects observed
- Decreased frequency of undesired symptoms over time
- Reductions in daily opioid medication doses *(3 months and beyond)*

Study Limitations

- No control group
- Dosing unknown
- Hundreds lost to follow-up
- Biases (recall, expectation, selection/volunteer)
- Data collection methods
- Strategies to retain patients long-term
- Lack of standardized reporting for adverse events

Final Thoughts

1. Cannabis use for chronic pain is expected to increase.
2. Between preclinical and clinical studies, discrepancies regarding efficacy exists.
3. Given the limitations to translational cannabis research, a broader definition of evidence is needed.
4. Observational studies may serve as "real-world" evidence, providing insight to cannabis efficacy and safety.

Thank You & Contact Information

To email
Dr. Asike

References

SESSION SIX

To view page
on web browser