Medical Cannabis: Cannabinoid Pharmacology, Clinical Science & Public Health Impact

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Outline

- Cannabinoid pharmacology
- Overview of cannabidiol (CBD)
- Overview of medical cannabis
- Impact on opioid use/misuse, opioid crisis
- Discussion/Q&A (after next presenter)
Cannabinoid Pharmacology
Cannabinoids

- There are approximately 500 phytochemicals that naturally occur in the cannabis (marijuana) plant

- The dozens of chemicals that are unique to the cannabis plant are called cannabinoids

- Present in the plant’s buds (leaves, stalks, seeds)

- There are several classes of plant-derived cannabinoids, including:
  - $\Delta^9$ tetrahydrocannabinol (THC)
  - cannabidiol (CBD, CBDV)
  - cannabinol (CBN, CBDL)
  - cannabichromenes (CBC)
  - cannabigerols (CBG)
  - Others: CBL, CBE, CBT
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Endocannabinoids

- Endogenous cannabinoids produced in the body called endocannabinoids

- Examples: Anandamide, 2-AG

- Endogenous ligands at the cannabinoid receptors (CB$_1$, CB$_2$)

- Present in both the CNS and periphery

- Involved in regulation of sleep, memory, inflammation, immune function, insulin sensitivity, fat and energy metabolism, reproduction (ovulation, implantation), expressed in breast milk

- Degraded by naturally occurring enzymes: FAAH (fatty acid amide hydrolase), MAGL (monoacylglycerol lipase)

- THC and other cannabinoids exert their action through this system
Cannabinoid Receptors

Cannabinoids exert action at cannabinoid receptors: \( \text{CB}_1 \) and \( \text{CB}_2 \)

**\( \text{CB}_1 \) receptor**
- one of the most abundant GPCR receptor in the CNS
- \( \text{CB}_1 \) agonists produce psychoactive effects (“high”)
- also located in the periphery (GI tract, cardiac tissue, reproductive system, fat tissue, skeletal muscle)

**\( \text{CB}_2 \) receptor**
- primarily located in the periphery, regulation of immune function
- also small number of receptors present in the brain
Δ⁹ tetrahydrocannabinol (THC)

- THC is the primary chemical that produces the “high” from cannabis.

- THC naturally occurs in cannabis plant; however, due to selective plant breeding, THC is now present at very high concentrations.

- Physiological effects include: tachycardia (dose-dependent), sedation, euphoria/“high”, red/bloodshot eyes, increased hunger, relaxation; also anxiety/panic in some conditions; can produce antiemetic effects; repeated use - cannabinoid hyperemesis syndrome.

- **Does not produce overdose, deaths in adults** – has partial agonist activity at the receptors (CB₁, CB₂)
  - however, can be highly toxic in children, animals.
Cannabidiol (CBD)

- Atypical cannabinoid – does not bind to cannabinoid receptors (CB₁, CB₂)

- Activity at adenosine, glycine, 5-HT₁A; regulates sodium channel activity

- Naturally occurring in the cannabis plant (small concentrations)

- Extraction from plant material or chemical synthesis to yield pure CBD

- Does not appear to produce a high or other effects that suggest it will be misused (even at very high doses)

- Appears to be generally safe/well-tolerated, but no data on long-term exposure are available; no studies of physical dependence are available
CBD Therapeutic Use Overview
CBD Therapeutic Effects: Rare Seizure Disorders

Positive efficacy findings for two forms of severe, intractable, childhood-onset, treatment-resistant seizure disorders

- Dravet Syndrome
- Lenox-Gastaut Syndrome

Epidiolex: US FDA approved for Dravet & LGS

- Oral solution (100 mg/mL)
- 2.5 mg/kg/day – 20 mg/kg/day
- Schedule V (does not apply to other formulations)
CBD Therapeutic Targets

Studies are published or underway to examine CBD for:

- Graft versus host disease, multiple sclerosis, chronic, acute and neuropathic pain, schizophrenia, early psychosis, anxiety, substance use disorders, bipolar/depressive disorders, PTSD and alcohol use disorder, vascular and cognitive function, Prader-Willi Syndrome, Fragile X Syndrome, Autism Spectrum Disorder, Sturge-Weber Syndrome, Parkinson’s Disease, Huntington’s Disease, Crohn’s Disease, ulcerative colitis, fatty liver disease, solid tumor cancer, type II diabetes

Insufficient data are available to support efficacy for these conditions

No data available to indicate CBD acts as an analgesic
Integrity of CBD Products

The FDA-approved product (Epidiolex) is pure CBD, with trace other cannabinoids.

Other sources of CBD are currently unregulated:
- unknown contents/unknown sterility (no mandated chemical/contaminant analyses)
- companies may provide analyses (posted online or by request); customers should ask for report/certificate of analysis

The FDA has independently tested CBD products and reported that some do not contain any CBD.

Researchers have also tested a wide variety of CBD online:
- 70% of products were mislabeled
- 18/84 samples tested contained THC (up to 6.4 mg/mL)

One very popular brand contains 3 mg/mL THC; manufacturers “recommend” several doses per day and indicate that it is safe for children.
Medical Cannabis Overview
“Medical Marijuana” or Medical Cannabis is a non-specific blanket term that encompasses the use of any cannabinoid for a medical condition. Physicians/providers are only permitted to “recommend” medical cannabis to patients; due to federal law, it cannot be prescribed.
Medical Cannabis Availability

Currently, 33 states and Washington DC allow for some type of medical cannabis/medical marijuana program.

11 states have legalized recreational cannabis and offer it in dispensaries/marketplaces/storefronts; Washington DC has effectively legalized, but does not offer a legal/sanctioned source of cannabis (no storefronts).

Michigan and Illinois are the only states in the Mid-West that have legalized recreational cannabis.
33 Legal Medical Marijuana States & DC
11 Legal Recreational Marijuana States & DC

States with Legal Medical Marijuana

States with Legal Medical & Recreational Marijuana
Medical Cannabis Products

There are no real differences in cannabis plant material available for medical use vs. recreational use.

Recreational dispensaries offer high-potency THC cannabis (20% and higher THC concentration), high potency oils/topicals and edibles; same products are available in medical dispensaries.
THC Concentrations Increasing

High THC content cannabis is now widely available in street/black market, medicinal and legalized recreational cannabis.

Mean THC content of confiscated cannabis in the US:

- 1970s: 1 - 2%
- 1990s: 3 - 4%
- 2010s: 10 – 15%
- 2019: 17%

Medical marijuana: 15 - 20%

Legal recreational marijuana: 15 - 20%+

Legal THC oils : 50-80%+

Legal THC concentrates: 70 – 80%+

Generally low levels of CBD (0.1-0.2%) in most cannabis; although some have moderate/high amounts of CBD (5-10% in some cases)
Medical Cannabis Practice

The medical conditions that qualify a patient for medical cannabis referrals varies from state to state

California allows physicians to recommend for any condition

West Virginia and Pennsylvania have relatively short list of conditions
  - ALS, cancer, MS, Parkinson’s Disease, PTSD, sickle cell, intractable pain, terminal illness

Some states do not allow plant material (no buds, smokeable items) - only oils, liquids, topicals (none of these are FDA approved; rely on third party testing)

Kentucky is considering medical cannabis – several legislators have voiced their support of passing legislation
  - need to carefully consider what conditions would be permitted; what products would be allowed
Δ⁹ tetrahydrocannabinol (THC)

Synthetic THC is present in two FDA-approved medications; approved for the treatment of nausea, vomiting, appetite loss associated with chemotherapy

- Cesamet® (nabilone)
- Marinol® (dronabinol)

Contains only THC, no other cannabinoids – no CBD, no other cannabinoid chemicals; slow/variable onset; variable absorption

Some patients report that eating THC edibles and smoking cannabis are better than these oral treatments, but no controlled studies have been conducted
Clinical Science: Medical Cannabis
Cannabinoids and Pain

Does cannabis relieve pain?
Small Signal for Analgesic Effects

Cannabinoids for Medical Use: A Systematic Review and Meta-Analysis
JAMA, 2015 : Whiting et al.

Small reduction in patient reports of chronic pain (79 trials included)
- 37% vs. 30% (THC-based cannabinoids vs. placebo)
- No improvement in QOL
- AEs common (e.g., vomiting, confusion)

### Improvement in Pain With Cannabinoid vs Placebo by Study

<table>
<thead>
<tr>
<th>Cannabinoid Events</th>
<th>Placebo Events</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>No.</td>
<td>Total No.</td>
<td>No.</td>
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<tr>
<td>Tetrahydrocannabinol (smoked)</td>
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<td>Abrams et al, 77 2007</td>
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<td>GW Pharmaceuticals, 22 2005</td>
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<td>Johnson et al, 69 2010</td>
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<td>Langford et al, 65 2013</td>
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<tr>
<td>Nurmikko et al, 76 2007</td>
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<td>Portenoy et al, 67 2012</td>
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<tr>
<td>Selvarajah et al, 70 2010</td>
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<td>Serpell et al, 88 2014</td>
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<tr>
<td>Subtotal $I^2 = 44.5%$, ($P = .94$)</td>
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<td>Overall $I^2 = 47.6%$, ($P = .64$)</td>
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Favors Placebo Favors Cannabinoid Weight, %
6.51
19.02
10.87
20.19
9.84
14.04
4.63
14.91
93.49
100.00

Odds Ratio (95% CI)
Small Signal for Analgesic Effects

National Academies of Sciences, Engineering and Medicine 2017 Report

- Examined 5 reviews of the literature

- Modest analgesic effect on pain symptoms in adults with chronic pain

  - Modest self-reported improvement in MS spasticity; antiemetic for chemotherapy NV
Minimal to No Analgesia

Cannabis-based medicines for neuropathic pain in adults
*Mücke et al., 2018; Cochrane Review*

- Reviewed 16 studies
- Patients achieving 50% or greater reduction with cannabinoids vs. placebo = 20% vs. 17%
- Patients achieving 30% reduction = 39% vs. 33%
- More AEs = 61% vs. 29%
- More participants withdrew due to AEs = 10% vs. 5%

- Conclusion – benefit may not outweigh harms
- Patients achieving 30% reduction in pain = 29% vs. 26%
- Minimal effect on pain intensity
- AEs = 81% vs. 66%

- Conclusion – evidence of benefits is limited; unlikely that cannabinoids are highly effective for CNCP
Medical Cannabis & Potential Impact on Opioid Use
Medical Cannabis & Opioids

Can medical cannabis replace opioids?
Medical Cannabis & Opioids

There have been several *correlational*, population-level studies that have received widespread attention:

- suggest presence of medical cannabis laws decrease the total number of opioid doses prescribed (Bradford & Bradford, 2017; 2019)

- opioid overdose deaths declined by 25% following the passage of medical cannabis legislation (Bachhuber et al., 2014)
Critical issues to consider:

- the data reported **does not examine effects on an individual level**
- there is no evidence that patients taking medical cannabis were the same people who received fewer opioid prescriptions or were protected from overdose
- for example, we do not know if the people who died from overdoses were the ones smoking cannabis or not – no analysis of death records to date
  - *we are starting to look at Kentucky data/death certificates to try to better answer this question*
- newer studies are showing the opposite effect – medical cannabis laws are increase opioid overdose deaths
- overall, using this type of population data cannot answer this question; numerous other (non-pharmacological) factors could account for these coinciding changes (Rx monitoring programs, naloxone distribution, crack-down on opioid prescribing)
UK Laboratory Study

Can THC reduce the opioid dose needed for pain relief (opioid sparing)? Can it decrease opioid side effects or sedation/impairment?

Placebo-controlled, double-blind, randomized human laboratory study

Participants were healthy adults, ages 18-50, without chronic or acute pain, no current drug misuse (no cannabinoid or opioid misuse in past 60 days)

Oral doses of oxycodone (0, 5, 10 mg), dronabinol [FDA-approved THC] (0, 2.5, 5 mg) and their combination

Participants exposed to painful stimulation (cold water, pressure, heat); we examined how the medications relieved pain; how the drugs made them feel
Pressure Algometer

![Graph showing the relationship between Peak Tolerance (kPa) and Oxycodone (mg) with THC (mg) as a variable.](graph.png)

- **Peak Tolerance (kPa)** vs. **Oxycodone (mg)**
- **THC (mg)**:
  - ○ 0 mg
  - △ 2.5 mg
“Do you feel any DRUG EFFECT?”
UK Laboratory Study

The results indicated that THC did not enhance the analgesic effects of the opioid.

However, THC did increase the opioid subjective effects, increased ratings of feeling high and liking the drug effect.

Not ideal results for a pain relieving drug.

These participants were not pain patients – THC and opioids may have a different effect in those with chronic pain.
Can Cannabis Replace Opioids?

Strongest data to date suggests *that medical cannabis use may be detrimental to pain patients taking opioid analgesics*

**POINT study conducted in Australia (Campbell et al., 2018; *Lancet*)**
- 1514 patients; chronic non-cancer pain, prescribed opioids
- collected data annually for 4 years
- examined pain, anxiety, depression and opioid use outcomes in those who elected to use cannabis for pain
  - *cannabis worsened patient outcomes*
- greater pain severity, greater pain interference in their daily activities, and greater anxiety scores
- cannabis did not reduce opioid doses
- no change the number of patients who were able to stop taking opioids
Can medical cannabis help solve the opioid epidemic?

Medical Marijuana Treatment for Opiate Addiction

America's Painkiller Epidemic: Is medicinal cannabis the answer to fewer deaths?
Some states (examples: New York, Illinois, Pennsylvania) list opioid use disorder as a qualifying condition for medical cannabis access.

No clear/strong evidence that cannabis can help any aspect of the opioid crisis.

We know virtually nothing about the interactions of opioids/cannabinoids in humans (pharmacological interactions; pain, abuse potential outcomes).
We do not know if cannabinoids increase opioid-induced respiratory depression? Or if they can potentially safeguard against this (and decrease the chances of overdose)?

We do not know if smoking cannabis increases the abuse potential of opioids (does cannabis make you crave opioids more, take more opioids)?

Currently awarded grant from the National Institute on Drug Abuse to study these questions in a series of inpatient studies in humans; administering high potency cannabis with opioids
Medical Cannabis & Opioid Use Disorder

There are several FDA-approved medications for opioid use disorder that have reliably shown to be highly effective

- protect from overdose, decrease illicit drug use, decrease opioid misuse, decrease disease transmission

Reckless to suggest that cannabinoids should be used for this disorder when 1) there is no evidence to suggest it is effective, 2) there are FDA-approved medications for this condition
Overall Lack of Controlled Studies

Cannabis is still a Schedule I drug on a federal level.

Researchers subjected to enormous amount of regulation to study it; has lead to few controlled studies to study its therapeutic effects.

It could be effective for several conditions, but without data/scientific evidence, it is difficult to state (particularly the medical community) what it should be used for (catch 22).

Public use of cannabinoids has far outpaced the science.

This has allowed anecdote and pseudoscience to prosper.
Find Your Strain
www.mmjdoctor.com

Happy Feeling
- Sour Diesel
- Girl Scout Cookies
- OG Kush
- Grand Daddy Purple
- Chemdawg

Relieves Pain
- AK-47
- Trainwreck
- White Rhino
- Purple Haze
- Afghan Kush

Fight Depression
- OG Kush
- White Widow
- Northern Lights
- Super Silver Haze
- Maui Wowie

Energetic
- Durban Poison
- Jack Herer
- Pineapple Express
- Lemon Haze
- Strawberry Cough

Creativity
- Sour Diesel
- Cherry Pie
- Super Lemon Haze
- Blueberry Gum
- Tangie

Boosts Appetite
- Purple Kush
- Lemon Skunk
- Skywalker
- Orange Kush
- Purple Haze

Sleep Better
- Grape Ape
- Skywalker
- Berry White
- Ritual Kush
- GT 13

Relieves Stress
- Durban Poison
- Sour Diesel
- Blue Dream
- Green Crack
- Blue Cheese

Cannabis, a solution to the opioid epidemic

Cannabis Man

The Nervous System
Aids in sleep.
CBN

Reduced seizures & convulsions.
CBD

Tranquilizing.
CBD

Anxiety releiver.
CBD

Digestive System
Appetite suppressant.
THC

Appetite stimulant.
THC

Reduces contractions in the small intestines.
CBD

Circulatory System
Reduces risk of artery blockage - anti-ischemic.
CBD

Increases cerebral blood flow.
THC CBD

Whole Body Relief & Protection
Inhibits cell growth in tumors and cancer cells.
THC CBD CBG CBC

Reduces or eliminates pain.
THC CBD CBN CBC

Mary's Medicinals
MarysMedicinals.com
Overall Lack of Controlled Studies

We know very little about the best dose, strain, cannabinoid ratio (THC:CBD), route of administration that is effective for any condition (with very few exceptions related to FDA approved products)

There have not been enough high quality studies to determine what conditions it may help, what conditions may worsen with cannabinoid treatment

Questions for Kentucky as it considers medical cannabis: What conditions should qualify? Palliative or end-of-life care? Any intractable condition? Any serious medical condition? N/V associated with cancer treatment? How will impact the Kentucky’s opioid crisis?
Overall Conclusions

There are several conditions for which medical cannabis may be helpful; particularly in compassionate care and palliative care settings; relief for cancer patients/chemotherapy side effects

However, public demand for cannabinoid-based medications has far outpaced the science

There is no conclusive evidence that medical cannabis is a highly effective analgesic for pain; however, we are limited by the current state of research

No clear data on other therapeutic effects on anxiety, depression, PTSD, anti-cancer effects, etc. Medical cannabis could be beneficial, but there is no current evidence that it is an effective medicine (catch 22)

No evidence that cannabis is helpful in reducing opioid analgesic doses; however, there is evidence suggesting that it could increase pain (which could increase opioid dose requirements); no evidence that it is effective for opioid use disorder

More high-quality human research is needed to determine the therapeutic effects of cannabis for medical conditions
Questions

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THC Concentrates

- Available legally in recreational shops
- Very high THC content (75-90% and higher)
- Liquid, wax, semi-solid, solid forms available
- Terms: shatter, dabs, oils, wax, butter
Dangerous Non-Cannabis Products
Synthetic Cannabinoids (K2, Spice)

Chemicals contained in K2, Spice and Serenity are **synthetic, lab-made chemicals that do not occur in nature**

Very high affinity, full agonist at CB$_1$ and/or CB$_2$ (no ceiling on its effects)

Very dangerous – hallucinations, psychotic episodes, seizures, overdoses, coma, and sometimes death

Oftentimes used when someone wants to get high, but pass a drug test (need specialized tests to detect these chemicals)

Street drug not sold in dispensaries; **however, some vaping cartridges and CBD oils are now being laced with these chemicals (and bath salts/stimulants) - they are cheap; no regulation**
Vaping Related Illnesses

The CDC is reporting 530 confirmed and probable cases of severe lung disease (other estimates much higher)

Confirmed 7 deaths

Right now, illness linked to vaporizing nicotine and THC oil

Not linked to smoking marijuana or vaping marijuana plant material – all linked to vaping cartridges filled with “vape juice”

Nearly all of the products are un-regulated and contain a variety of chemicals (some of which may be toxic)

THC oil should never be inhaled (oils should never enter lungs)

Liquid when heated, but can turn more solidified when at lower temperatures; vitamin E acetate involved in some of the cases