The Search for the Magic Bullet: Can the Use of Medical Cannabis Decrease Opioid Use

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Brief History of Cannabis

- Cannabis plant and its uses date to as early as 4000 BC
- Named for Greek word for hemp, *kannabis*
- Long recorded history in medical writing; documented use for pain, dysentery, nausea / vomiting, spasms, and convulsions
- Rendered illegal in 1937
- Dropped from the US Pharmacopoeia in 1941

At the end of this presentation the participant will:
- Be able to discuss the pharmacology of THC & CBD
- Demonstrate an understanding of the “entourage effect” of cannabis
- Appreciate how the use of cannabis can decrease pain for patients with chronic noncancer pain (CNCP)
- Appreciate how the use of cannabis can decrease the amount of opioid medication utilized in patients with CNCP
Brief History of Cannabis in the US

- 1970 - Controlled Substances Act classified marijuana as a drug with “no accepted medical use”; ie: Schedule I
- 1976 - Federal Court rules Robert Randall’s use of marijuana a “medical necessity”
- 2018 - 29 states and the District of Columbia have approved medical cannabis programs and 9 states and Washington, DC have legalized for cannabis adult for recreational use.
Endocannabinoid System

https://www.youtube.com/watch?v=Vtc11kRinf4
The Medical Cannabis System

- The endocannabinoid system
  - Innate biologic system
  - Responsible for regulation of multiple body systems
  - CB1 and CB2 receptors throughout the body
  - No receptors in brainstem

- Clinical data available on the use of cannabis to treat symptoms related to serious medical conditions
- Cannabis may provide relief for patients whose symptoms are unrelieved by other means
Cannabinoid Components

- Composed of up to 400 components, including non-intoxicating components
  - 120 terpenoids: aromatic compounds
  - 21 flavonoids: antioxidants
  - 11 plant sterols (seed)
  - 22 fatty acids

- THC and CBD are the two main studied components of cannabis out of 60-100 active cannabinoids

- CBD can mitigate adverse effects of THC


Endocannabinoids

- Natural substances produced by the body
- Bind to receptors throughout the body
- No receptors in brainstem
- Exogenous cannabis plant has > 60 cannabinoids
THC (delta-9-tetra hydrocannabinol)

- euphoric
- stimulant
- muscle-relaxing
- analgesic
- anti-emetic
- appetite stimulating
- lowers intra-ocular pressure
- A High THC is 15-25%
**CBD (Cannabidiol)**

**Researched Attributes**

- Anxiolytic
- Anti-psychotic
- Anticonvulsant
- Anti-oxidant
- Anti-inflammatory
- Anti-ischemic
- Anti-emetic
- Anti-tumor
- Neuroprotection

*CBD mitigates the psychoactive side effect of THC*
- A high CBD is 5-15%
Endocannabinoid System & Pain
Endocannabinoid System & Pain

- N and P/Q VSCC blockade
- K-ir potentiation
- VSSC blockade
- mapKinase activation
- mast cell inhibition
- modulation of GABAergic, glycinergic, and glutamatergic neurotransmission


Potential Therapeutic Effects/Benefits

THC (delta-9-tetrahydrocannabinol)
* Intoxicating effects
* Appetite stimulant
* Decreased intraocular pressure
* Analgesic/neuropathic pain
* Antispasmodic
* Antiemetic

CBD (cannabidiol)
* Not intoxicating
* Analgesic/neuropathic pain
* Antipsychotic effects
* Anticonvulsant
* Neuro-protective effects
* Antispasmodic
* Antiemetic
Utility in Pain

- Prevention of paclitaxel-induced painful neuropathy
- Medication overuse headache, migraine, and cluster
- Cancer pain
- Neuropathic pain
- Osteoarthritis
- Central sensitization
- Brachial plexus avulsion
- Fibromyalgia

Oral THC Pharmacology

- Low (6-20%) and variable bioavailability
- Peak plasma within 1-6 and may remain elevated for several hours
- Initially oxidized in liver to 11-OH-THC, a potent psychoactive metabolite
- Further oxidation of 11-OH-THC leads to elimination products (urine and feces)
- Terminal half life 20-30 hrs
Smoked THC Pharmacology

- Rapidly absorbed into bloodstream and redistributed
- Considerable amount of dose lost in smoking
- Peak blood levels achieved at end of smoking, decline rapidly over 30 minutes
- Smoking achieves higher peak concentration but shorter duration of effect
- Smaller amounts of 11 OH-THC formed
Toxicity
- No lethal overdoses reported from cannabis alone
- Less toxicity/lethality ratio than alcohol, opiates, barbiturates, and some common medications

Dependence and Withdrawal
- Estimates of dependence are highly controversial
- Mild, short-lived feelings of withdrawal occur for some

Other Drug Use
- No conclusive evidence cannabis leads to other substances of abuse or that medical programs increase use among general population
- Typical “gateways” are tobacco and alcohol

Common Questions
Potential Adverse Effects

- **Central Nervous System**
  - Can be treatment limiting – generally see anxiety/paranoia
  - Strains with lower THC and higher CBD content less psychoactive

- **Neuropsychiatric**
  - Teens and younger populations – questions regarding cognitive development, memory, and psychiatric illness

- **Other – General**
  - Cardiovascular, appetite, nausea, hyperemesis syndrome, headache, decreased coordination/muscle strength, thirst/dry mouth, red/dry eyes
Pharmaceutical Preparations

- **Dronabinol (Marinol)**, is synthetic Δ9-tetrahydrocannabinol (THC), used as an appetite stimulant, antiemetic, and analgesic. Approved in 1986 for N&V from Chemotherapy; AIDS anorexia in 1992

- **Nabilone (Cesamet)**, a synthetic cannabinoid and an analog of Marinol. It is Schedule II unlike Marinol, which is Schedule III

- **Nabiximols (Sativex)**, a cannabinoid extract oral spray containing THC, CBD, and other cannabinoids used for neuropathic pain and spasticity in 22 countries including England, Canada, and Spain (not available in the US). Sativex is a whole-plant cannabinoid medicine.
Marinol is synthetic THC

- Only one of many cannabinoids in the cannabis plant ("Entourage Effect")
- The psychoactive component may present a duration of action that is not acceptable to the patient

Many other cannabinoids in the plant have important effects

- Anti-inflammatory, anti-nausea, neuroprotection

Different strains of cannabis have varying THC content and various effects on symptoms

If used for nausea and vomiting, patient may have difficulty tolerating oral medications
Safety of Pharmaceutical Cannabinoids

- Low abuse potential of prescription cannabinoids
  - Dronabinol (Calhoun 1998)
  - Nabilone (Ware 2010)
  - Nabiximols (Robson 2011)
- No evidence of tolerance (Rog 2007, Serpell, 2013)
**Adverse Effects**

- CNS side effects primarily anxiety and paranoia
- Strains with lower THC content less psychoactive

**General physical effects**
- Changes in appetite, thirst, nausea, headache, decreased coordination, reduced muscle strength, dry mouth, and sensitivities including redness and dryness of the eyes.

**Toxicity**
- No lethal overdoses reported with non derivative products
- Less toxicity/lethality ratio than alcohol, opiates, barbiturates, and some common meds
Acute Drug Interactions

- Acute medical risk of THC are rather low
- Fatal overdose with cannabis alone has not been reported
- Additive effects of cannabis, anticholinergics and CNS depressants
  - (e.g., sedation, dry mouth, dizziness, and confusion)
  - Smoking itself (cannabis or tobacco) induces CYP 1A2
    - May increase clearance of anti-psychotics and anti-depressants
    - Metabolized by P450, little evidence supporting drug-drug interaction
  - Chronic opiate users have seen a potential reduction of doses when in conjunction with medical cannabis
Cannabinoid-Opioid Interaction in Chronic Pain

- Objectives
  - Evaluate effect of vaporized cannabis on Blood levels of prescribed opiates (SR morphine and SR Oxycodone)
  - Determine the short-term side effects of co-administration of cannabis and opioids
  - Assess effect of vaporized cannabis on level of Chronic pain
- N = 21
- Funded in part by NIDA and NIH CRC grants
Cannabinoid-Opioid Interaction in Chronic Pain

* **Study**
  * 21 pts with chronic pain, on twice-daily doses of sustained release morphine or oxycodone were admitted for a 5-day inpatient stay
  * Asked to inhale vaporized cannabis in the evening of day 1, three times a day on days 2–4, and in the morning of day 5
  * The extent of chronic pain was assessed daily

* **Results**
  * No significant change in the AUC for either morphine or oxycodone after exposure to cannabis
  * Pain was significantly decreased (average 27%) after the addition of vaporized cannabis

Cannabinoid-Opioid Interaction in Chronic Pain

- Co-administration of vaporized cannabis with oral sustained release opiates is safe
- Co-administration of vaporized cannabis in subjects on stable doses of morphine or oxycodone appears to enhance analgesia
- Co-administration of vaporized cannabis trends towards lowering concentration of the opioids of the opioids
  * The PK effects would be expected to reduce the analgesic effects of opioids.
  * The effects of vaporized cannabis to enhance opioid analgesia occurs by a pharmacodynamic, not a pharmacokinetic effect.

Cannabis & Opioid Use/Abuse

- Cannabis use common among opioid-dependent individuals
  - Range from 20% to 95%
  - Cannabis use associated with drug dealing and needle sharing
- Cannabis effects on treatment for opioid-dependence
  - Cannabis use associated with faster relapse to alcohol, cocaine, and heroin use
  - In chronic opioid therapy for pain, cannabis use was a positive predictor of future opioid misuse
  - Cannabis use strongly associated with increased risk for other substance use and dependence
  - These were self-selected cannabis users

Many studies have demonstrated cannabis use associated with positive treatment prognosis among opioid-dependent cohorts

- Cannabis abuse & dependence were predictive of decreased heroin & cocaine use during treatment
- Intermittent use of cannabis was associated with a lower percentage of positive opioid UDS and improved medication compliance on naltrexone
- Cannabis improved opioid-dependence treatment retention
- Cannabis use may benefit opioid users in withdrawal
- These were self-selected cannabis users

The substance-dependent population may differ significantly from drug naïve or recreational substance users.

Correlation with medical cannabis users is difficult but suggests that aside from direct, pain-related benefits of cannabis in delaying initiation and adjunctive pain-relief, cannabis may provide positive effects in opioid abusers.

Cannabinoid-Opioid Interaction

- Receptor systems of both cannabinoids and opioids are known to mediate common signaling pathways
- Drugs that target both the cannabinoid and morphine receptor systems possess shared pharmacological profiles
  - Agonists of both receptor types have been shown to cause pain relief, sedation, hypotension, motor depression, and drug reward/reinforcement
Cannabinoid-Opioid Interaction

- Studies demonstrate cross-tolerance, mutual potentiation, and receptor cross-talk
  - Implies that pain relief from cannabinoids are more than just psychotropic-based
- Cannabinoids may modulate opioid function at a number of different levels within the cell
  - Potential for additive pain relief with combination of opioids & cannabinoids
Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in The United States 1999-2010

- Time series analysis of medical cannabis laws and state-level death certificate data in the US from 1999 to 2010; all 50 states included
- States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95%CI, -37% to -9%, P = 0.003)
- Examination of the association between medical cannabis laws and opioid analgesic overdose mortality in each year of implementation of the law showed a lower rate of OD mortality over time that generally strengthened over time

The endocannabinoid system is an innate biologic system responsible for regulation of body multiple systems.

There is clinical data on the use of cannabis to treat symptoms related to serious medical conditions.

Cannabis may provide relief for patients suffering from illness or disease unrelieved by other modalities.

Recommending a patient for the program is protected under state law.
The use of cannabis has a place in the treatment of CNCP

- The use of cannabis may decrease the use of opioid medication in patients with CNCP
- Cannabis has a favorable safety profile