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## Inaugural National Conference

**December 3 – 5, 2020**

VIRTUAL CONFERENCE



**RhAPP**

RHEUMATOLOGY ADVANCED  
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# Marijuana

## All the Stuff You Always Wanted to Know

Chris Kottenstette, PA-C

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# Faculty Disclosures

## **Chris Kottenstette, PA-C**

- None

# Our Knowledge About the Biology of Marijuana and Cannabinoids Allows Us to Make Some General Conclusions

- Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- The natural role of cannabinoids in immune systems is likely multi-faceted and remains unclear.
- The brain develops tolerance to cannabinoids.
- Animal research demonstrates the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
- Withdrawal symptoms can be observed in animals but appear to be mild compared to opiates or benzodiazepines, such as diazepam (Valium).

# The Different Cannabinoid Receptor Types Found in the Body Appear to Play Different Roles in Normal Human Physiology

- Some effects of cannabinoids appear to be independent of CB receptors
- There is a variety of mechanisms through which cannabinoids can influence human physiology
- There are a variety of potential therapeutic uses for drugs that might act selectively on different cannabinoid systems (CB1, CB2, Valininioid)

All the Cannabinoids Are Lipophilic – They Are Highly Soluble in Fatty Fluids and Tissues But Not in Water. Indeed, THC Is So Lipophilic That It Is Aptly Described As “Greasy.”

**Table 1.5** Cannabinoids Identified in Marijuana

Cannabinoid Group	Common Abbreviation	No. of Known Variants in Each Group
$\Delta^9$ -Tetrahydrocannabinol	$\Delta^9$ -THC	9
$\Delta^8$ -Tetrahydrocannabinol	$\Delta^8$ -THC	2
Cannabichromene	CBC	5
Cannabicyclol	CBL	3
Cannabidiol	CBD	7
Cannabielsoin	CBE	5
Cannabigerol	CBG	6
Cannabinidiol	CBND	2
Cannabinol	CBN	7
Cannabitriol	CBT	9
Miscellaneous types		11
Total		66

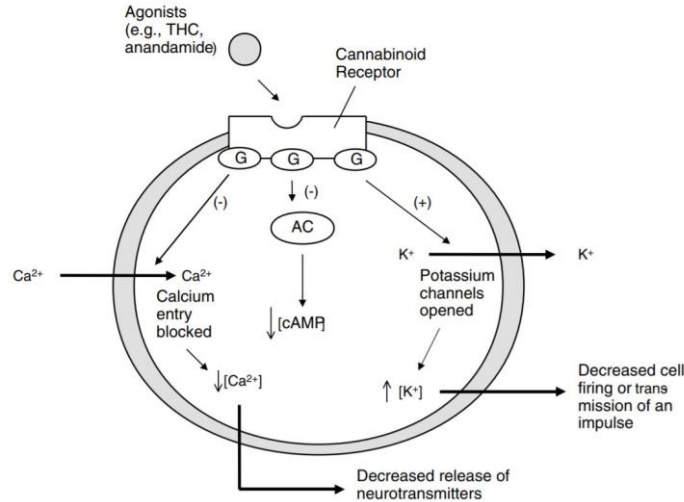
# Minimizing Anxiety

- There are numerous anecdotal reports claiming that marijuana with relatively **higher ratios of THC:CBD** is **less likely to induce anxiety** in the user than marijuana with low THC:CBD ratios; but, taken together, the results published thus far are inconclusive.

# CBD Increases THC High

- The most important effect of CBD seems to be its interference with drug metabolism, including  $\Delta$ 9-THC metabolism in the liver.
- It exerts that effect by inactivating cytochrome P450s, which are the most important class of enzymes that metabolize drugs. Like many P450 inactivators, CBD can also induce P450s after repeated doses.
- Experiments in which mice were treated with CBD followed by THC showed that **CBD treatment was associated with a substantial increase in brain concentrations of THC and its major metabolites, most likely because it decreased the rate of clearance of THC from the body.**

# THC Acts as a Neuroleptic



**FIGURE 2.3** Cannabinoid agonists trigger a series of reactions within cells. Cannabinoid receptors are embedded in the cell membrane, where they are coupled to G proteins (G) and the enzyme adenylyl cyclase (AC). Receptors are activated when they bind to ligands, such as anandamide or THC in this case. This triggers a variety of reactions, including inhibition (-) of AC, which decreases the production of cAMP and cellular activities dependent on cAMP; opening of potassium ( $K^+$ ) channels, which decreases cell firing; and closing of calcium ( $Ca^{2+}$ ) channels, which decreases the release of neurotransmitters. Each of those changes can influence cellular communication.

# Cannabinoids MOA

- Although similar to opiate analgesia, cannabinoid analgesia is not mediated by opioid receptors.
- Morphine and cannabinoids sometimes act synergistically, and opioid antagonists generally have no effect on cannabinoid-induced analgesia.
- However, a kappa-receptor antagonist has been shown to attenuate spinal, but not supraspinal, cannabinoid analgesia.
  - Kappa opioid receptors constitute one of the three major types of opioid receptors; the other two types are mu and delta receptors.

# Cannabinoids MOA

- Cannabinoids decrease the response of immediate-early genes (genes that are activated in the early or immediate stage of response to a broad range of cellular stimuli) to noxious stimuli in the spinal cord, decrease response of pain neurons in the spinal cord, and decrease the responsiveness of pain neurons in the ventral posterolateral nucleus of the thalamus.
- Current data suggest that the endogenous cannabinoid analgesic system might offer protection against the long-lasting central hyperalgesia and allodynia that sometimes follow skin or nerve injuries.
- These results raise the possibility that therapeutic interventions that alter the levels of endogenous cannabinoids might be useful for managing pain in humans.

# Cannabinoids MOA

- Chronic administration of cannabinoids to animals results in tolerance to many of the acute effects of THC, including:
  - Memory disruption
  - Decreased locomotion
  - Hypothermia
  - Neuroendocrine effects
  - Analgesia
- Tolerance also develops to the cardiovascular and psychological effects of THC and marijuana in humans.
- It is difficult to extend the findings of short-term animal studies to human marijuana use.
  - To simulate long-term use, higher doses are used in animal studies than are normally achieved by smoking marijuana.
  - **For example, the average human will feel “high” after injection of THC at a level of 0.06 mg/kg, compared with the 10–20 mg/kg per day used in many chronic rat studies.**

# Cannabinoids – Reward and Dependence

- Experimental animals that are given the opportunity to self-administer cannabinoids generally do not choose to do so, which has led to the conclusion that they are not reinforcing and rewarding.
- However, behavioral and brain stimulation studies have shown that THC can be rewarding to animals.
  - The behavioral study used a “place preference” test, in which an animal is given repeated doses of a drug in one place, and is then given a choice between a place where it received the drug and a place where it did not. The animals chose the place where they received the THC.
  - These rewarding effects are highly dose dependent. In all models studied, cannabinoids are only rewarding at midrange; doses that are too low are not rewarding; doses that are too high can be aversive.

# Cannabinoids MOA

- This suggests that, under normal cannabis use, the **long half-life and slow elimination from the body** of THC and the residual bioactivity of its metabolite, 11-OH-THC, **can prevent substantial abstinence symptoms**.
- The rank order, from high to low, of CB2 mRNA levels in immune cells is B-cells > natural killer cells >> monocytes > polymorphonuclear neutrophil cells > T8 cells > T4 cells.
- In tonsils the CB2 receptors appear to be restricted to B-lymphocyte enriched areas.
- In contrast, CB1 receptors are mainly expressed in the central nervous system and, to a lesser extent, in several peripheral tissues such as adrenal gland, heart, lung, prostate, uterus, ovary, testis, bone marrow, thymus, and tonsils.

# Cannabinoids MOA

- Mice **pretreated with THC (8 mg/kg) one day before infection** with a sublethal dose of the pneumonia causing bacteria *Legionella pneumophila* and then treated again **one day after the infection** with THC developed symptoms of cytokine-mediated septic shock and **died**;
  - Control mice that were not pretreated with THC became immune to repeated infection and survived the bacterial challenge.
- **If only one injection of THC was given or doses less than 5 mg/kg were used**, all the mice survived the initial infection but failed to survive later challenge with a lethal dose of the bacteria; hence, **these mice failed to develop immune memory in response to the initial sublethal infection**.
  - Note that these are very high doses and are considerably higher than doses experienced by marijuana users
- Hence, **whether THC is immunosuppressive probably depends on the timing of THC exposure relative to an infection**.

# Cannabinoids MOA

- Cannabinoid drugs can modulate the production of cytokines, which are central to inflammatory processes in the body.
- **Several studies have shown directly that cannabinoids can be anti-inflammatory.**
- The possible link between experimental cannabinoid-induced analgesia and reported antiinflammatory effects of cannabinoids is important for potential therapeutic uses of cannabinoid drugs but has not yet been established.

# Effects on the Immune System

- Cell culture and animal studies have established cannabinoids as immunomodulators – that is, they increase some immune responses and decrease others.
- The variable responses depend on such experimental factors as drug dose, timing of delivery, and type of immune cell examined.
- Cannabinoids affect multiple cellular targets in the immune system and a variety of effector functions.
  - Many of the effects noted above appear to occur at concentrations over 5  $\mu\text{M}$  in vitro and over 5  $\mu\text{g}/\text{kg}$  in vivo.\*
  - By comparison, a **5-mg injection of THC into a person (about 0.06 mg/kg) is enough to produce strong psychoactive effects.**
- It should be emphasized, however, that little is known about the immune effects of chronic low dose exposure to cannabinoids.

# Cannabinoids MOA

- Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- The natural role of cannabinoids in immune systems is likely multi-faceted and remains unclear.
- The brain develops tolerance to cannabinoids.
- Animal research has demonstrated the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
- Withdrawal symptoms can be observed in animals but appear mild compared with those of withdrawal from opiates or benzodiazepines, such as diazepam (Valium).

# The Marijuana “High”

- The most commonly reported effects of smoked marijuana are a sense of well-being or euphoria and increased talkativeness and laughter alternating with periods of introspective dreaminess followed by lethargy and sleepiness.
- A characteristic feature of a marijuana “high” is a distortion in the sense of time associated with deficits in short-term memory and learning.
- A marijuana smoker typically has a sense of enhanced physical and emotional sensitivity, including a feeling of greater interpersonal closeness.
- The most obvious behavioral abnormality displayed by someone under the influence of marijuana is difficulty in carrying on an intelligible conversation, perhaps because of an inability to remember what was just said even a few words earlier.
- The high associated with marijuana is not generally claimed to be integral to its therapeutic value.
  - But mood enhancement, anxiety reduction, and mild sedation can be desirable qualities in medication – particularly for patients suffering pain and anxiety.

# Adverse Mood Reactions

- Anxiety and paranoia are the most common acute adverse reaction, others include:
  - Panic, depression, dysphoria, depersonalization, delusions, illusions, and hallucinations.
  - Of regular marijuana smokers, 17% report that they have experienced at least one of the symptoms, usually early in their use of marijuana.
    - Those observations are particularly relevant for the use of medical marijuana in people who have not previously used marijuana.

# MJ – Tolerance

- Tolerance to most of the effects of marijuana can develop rapidly after only a few doses, and it also disappears rapidly.
- Tolerance to large doses has been found to persist in experimental animals for long periods after cessation of drug use.
- Performance impairment is less among people who use marijuana heavily than it is among those who use marijuana only occasionally possibly because of tolerance.
- Heavy users tend to reach higher plasma concentrations of THC than light users after similar doses of THC, arguing against the possibility that heavy users show less performance impairment because they somehow absorb less THC (perhaps due to differences in smoking behavior).

# MJ – Time to Peak

- The oral and smoked doses were designed to deliver roughly equivalent amounts of THC to a subject.
- **Each smoked marijuana dose consisted of five 10-second puffs of a marijuana cigarette containing 3.1% THC.**
  - The pills contained 30 mg of THC.
- Both groups also received placebo drugs during other four-day periods.
- Although the dosing of the two groups was comparable, different routes of administration resulted in different patterns of drug effect.
- **The peak effect of smoked marijuana is usually felt within minutes and declines sharply after 30 minutes.**
- **The peak effect of oral THC is usually not felt until about an hour and lasts for several hours.**

# MJ – Withdrawal

- A distinctive marijuana and THC withdrawal syndrome has been identified.
  - But it is mild and subtle compared with the profound physical syndrome of alcohol or heroin withdrawal.
- The **symptoms of marijuana withdrawal include:**
- **Restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping.**
- In addition to those symptoms, two recent studies noted several more.
  - **Fatigue and illusions or hallucinations** after marijuana abstinence.

# MJ – Withdrawal

- Withdrawal symptoms have been observed in carefully controlled laboratory studies of people after use of both oral THC and smoked marijuana.
  - In one study, subjects were given **very high doses** of oral THC: **180–210 mg per day** for 10–20 days, roughly equivalent to smoking **9–10 2% THC cigarettes per day**.
  - During the **abstinence** period at the end of the study, the study subjects were **irritable and showed insomnia, runny nose, sweating, and decreased appetite**.
    - The withdrawal symptoms, however, were short lived. In four days they had abated.
  - The time course contrasts with that in another study in which lower doses of oral THC were used (80–120 mg/day for four days) and **withdrawal symptoms were still near maximal after four days**.

# MJ – Half-Life

- The half-life of THC in brain is about an hour.
- Although traces of THC can remain in the brain for much longer periods, the amounts are not physiologically significant.
- Thus, the lack of a withdrawal syndrome when THC is abruptly withdrawn without administration of a receptor-blocking drug is probably not due to a prolonged decline in brain concentrations.

# Opioid Use Decreased After MJ Legalization in Colorado

- We examined the association between the legalization of recreational marijuana and prescription opioid distribution in Colorado.
- Utah and Maryland, two states that had not legalized recreational marijuana, were selected for comparison.
- Prescription data reported to the Drug Enforcement Administration for nine opioids used for pain (e.g., fentanyl, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone) and two primarily for opioid use disorder (OUD, methadone and buprenorphine) from 2007 to 2017 were evaluated. **Analysis of the interval pre (2007–2012) versus post (2013–2017) marijuana legalization revealed statistically significant decreases for Colorado ( $P < 0.05$ ) and Maryland ( $P < 0.01$ ), but not Utah, for pain medications.**
- **There was a larger reduction from 2012 to 2017 in Colorado (–31.5%) than the other states (–14.2% to –23.5%).** Colorado had a significantly greater decrease in codeine and oxymorphone than the comparison states.
- The most prevalent opioids by morphine equivalents were oxycodone and methadone.
- Due to rapid and pronounced changes in prescription opioid distribution over the past decade, additional study with more states is needed to determine whether cannabis policy was associated with reductions in opioids used for chronic pain.

## Prescription Opioid Distribution after the Legalization of Recreational Marijuana in Colorado.

*Int. J. Environ. Res. Public Health.* **2020**; *17*, 3251; doi:10.3390/ijerph17093251. [www.mdpi.com/journal/ijerph](http://www.mdpi.com/journal/ijerph)

# THC Effects Similar to Gabapentin

- The aim of the present study was to examine a potential mechanism of action of gabapentin to manage cannabis-use disorders by determining the interoceptive effects of gabapentin in cannabis users discriminating  $\Delta 9$ -THC using a pharmacologically selective drug-discrimination procedure.
- Eight cannabis users learned to **discriminate 30 mg oral  $\Delta 9$ -THC from placebo** and **then received gabapentin (600 and 1200 mg),  $\Delta 9$ -THC (5, 15 and 30 mg) and placebo, alone and in combination.**
- Self-report, task performance and physiological measures were also collected.
- $\Delta 9$ -THC served as a discriminative stimulus, produced positive subjective effects, elevated heart rate and impaired psychomotor performance.
- **Both doses of gabapentin substituted for the  $\Delta 9$ -THC discriminative stimulus and engendered subjective and performance-impairing effects that overlapped with those of  $\Delta 9$ -THC when administered alone.**
- When administered concurrently, gabapentin shifted the discriminative-stimulus effects of  $\Delta 9$ -THC leftward/upward, and combinations of  $\Delta 9$ -THC and gabapentin generally produced larger effects on cannabinoid-sensitive outcomes relative to  $\Delta 9$ -THC alone. These results suggest that one mechanism by which gabapentin might facilitate cannabis abstinence is by producing effects that overlap with those of cannabinoids.

# The Endocannabinoid System

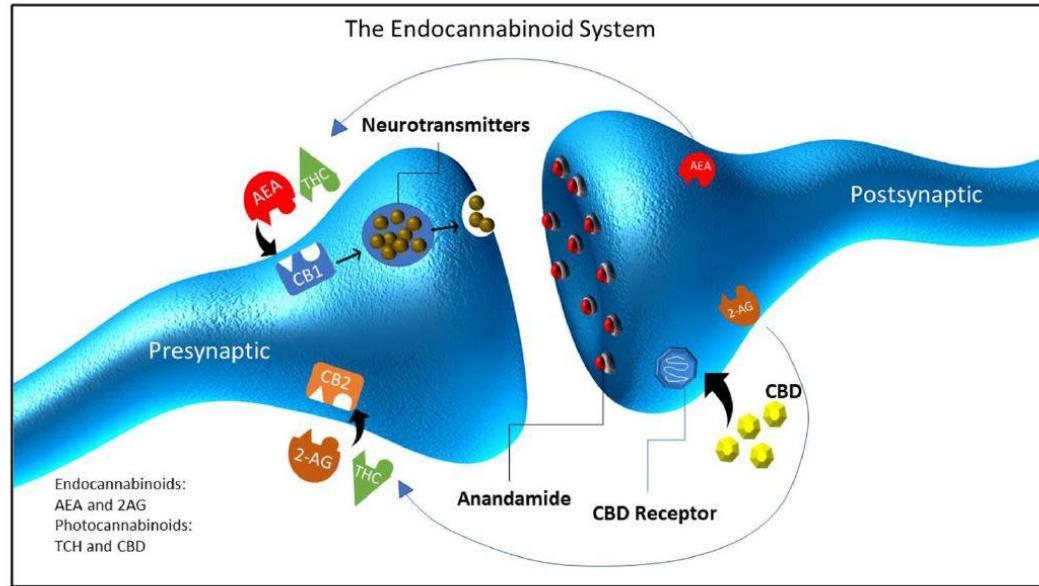


Figure 1. Endocannabinoid system.

## Schwerpunkt

Schmerz 2016 · 30:47–61  
DOI 10.1007/s00482-015-0084-3  
Published online: 14 January 2016  
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## **Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis)**

**A systematic review of randomized  
controlled trials**

Conclusions. Currently, there is insufficient evidence for recommendation for any cannabinoid preparations for symptom management in patients with chronic pain associated with rheumatic diseases.

# Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

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## Keywords

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

## Received

22 December 2010

## Accepted

7 March 2011

## Accepted Article

23 March 2011

Effective therapeutic options for patients living with chronic pain are limited. The pain relieving effect of cannabinoids remains unclear. A systematic review of randomized controlled trials (RCTs) examining cannabinoids in the treatment of chronic non-cancer pain was

Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis.



## Joint for joints: cannabinoids in the treatment of rheumatoid arthritis

*Torsten Lowin, Matthias Schneider, and Georg Pongratz*

### **Purpose of review**

An increasing number of patients with rheumatoid arthritis (RA) are using cannabis to treat their symptoms, although systematic studies regarding efficacy in RA are lacking. Within this review we will give an overview on the overall effects of cannabinoids in inflammation and why they might be useful in the treatment of RA.

### **Recent findings**

Peripherally, cannabinoids show anti-inflammatory effects by activating cannabinoid type 2 receptors (CB<sub>2</sub>) which decrease cytokine production and immune cell mobilization. In contrast, cannabinoid type 1 receptor (CB<sub>1</sub>) activation on immune cells is proinflammatory while CB<sub>1</sub> antagonism provides anti-inflammatory effects by increasing  $\beta_2$ -adrenergic signaling in the joint and secondary lymphoid organs. In addition, the nonpsychotropic cannabinoid, cannabidiol (CBD) demonstrated antiarthritic effects independent of cannabinoid receptors. In addition to controlling inflammation, cannabinoids reduce pain by activating central and peripheral CB<sub>1</sub>, peripheral CB<sub>2</sub> receptors and CBD-sensitive noncannabinoid receptor targets.

Cannabidiol (CBD) demonstrated antiarthritic effects independent of cannabinoid receptors. In addition to controlling inflammation, cannabinoids reduce pain by activating central and peripheral CB<sub>1</sub>, peripheral CB<sub>2</sub> receptors and CBD-sensitive noncannabinoid receptor targets.

# Inhibitory effect of synthetic cannabinoids on cytokine production in rheumatoid fibroblast-like synoviocytes

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## Abstract

### Objective

*To verify whether synthetic cannabinoids (CP55,940 and WIN55,212-2) are able to exert an anti-inflammatory effect on rheumatoid fibroblast-like synoviocytes (FLS) by down-regulating cytokine production, and determine whether this effect could be mediated by CB1/CB2 cannabinoid receptors.*

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### Methods

*Interleukin-6 (IL-6) and interleukin-8 (IL-8) were assayed in the supernatant from cultured FLS by ELISA method before and after 3 hours of incubation with CP55,940 (10 $\mu$ M) and WIN55,212-2 (10 $\mu$ M). Co-stimulation of cells with the cannabinoid receptor antagonists was performed to evaluate receptor involvement in cytokine modulation. All the experiments were conducted in basal conditions and after 1 hour pre-incubation with 0.1 ng/ml IL-1 $\beta$ . FLS expression of CB1 and CB2 receptor was studied by Western Blot analyses.*

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### Results

*Both CP55,940 and WIN55,212-2 induced a potent and significant reduction in IL-6 and IL-8 secretion from IL-1 $\beta$ -stimulated FLS. Although FLS express CB1 and CB2 receptor, cannabinoid receptor antagonists did not significantly modify the inhibition of cytokines secretion induced by CP55,940 and WIN55,212-2.*

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### Conclusions

*In vitro, CP55,940 and WIN55,212-2 exert a potent anti-inflammatory effect on rheumatoid FLS via a non-CB1/CB2 receptor mediated mechanism.*

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### Key words

Cannabinoids, rheumatoid arthritis, synoviocytes, cytokines.

# Thanks for Your Attention

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