# Medical Marijuana

Presented by

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# Disclosures

Nadia Fike, MD/PhD

No relevant financial or nonfinancial relationships to disclose.

# Questions

1. THC binds the CB1 receptor:
   True False

2. Cannabinoid use affects developing and adult brains in similar ways: True False

3. Cannabis is effective in management of intractable pediatric epilepsy syndromes:
   True False

# References


- (multiple) Epilepsia, 55(6), 783-802, 2014 (July)
- Koppel et al, Neurology, 82, 1556-1563, 2014 (April)
- Whalley et al, American herbal pharmacopia, therapeutic compendium, 2014 (March)
- Gilman et al, J. Neurosci, 34(16), 5529-5528, 2014 (Apr).

# Goals for Today

- What is (medical) marijuana, how and why does it have its effects on the brain
- Are there any special considerations for the developing brain
- Potential medical uses **- Epilepsy**

# Marijuana (Cannabis sativa)

- A typical Cannabis  sample contains more than 500 chemical compounds, and more than 80 cannabinoids, including:

    1. Tetrahydrocannabinol (**THC**) (4-25%)
    2. Cannabidiol (**CBD**) (1-4%)

    (etc – CBDV, CBN, CBC, CBG…)

# Endocannabinoid System

- Endogenous production of lipophilic cannabis-like agents by specific enzymes when triggered by neuronal depolarization.

- Endocannabinoids: Anandamide – **AEA** (arachidonoyl ethanolamide), **2-AG** (2-arachidonoyl glycerol);

- Receptors: **CB1** and **CB2**; g-protein receptors; activation inhibits adenylate cyclase and either inhibits voltage gated Ca channels or activates K channels

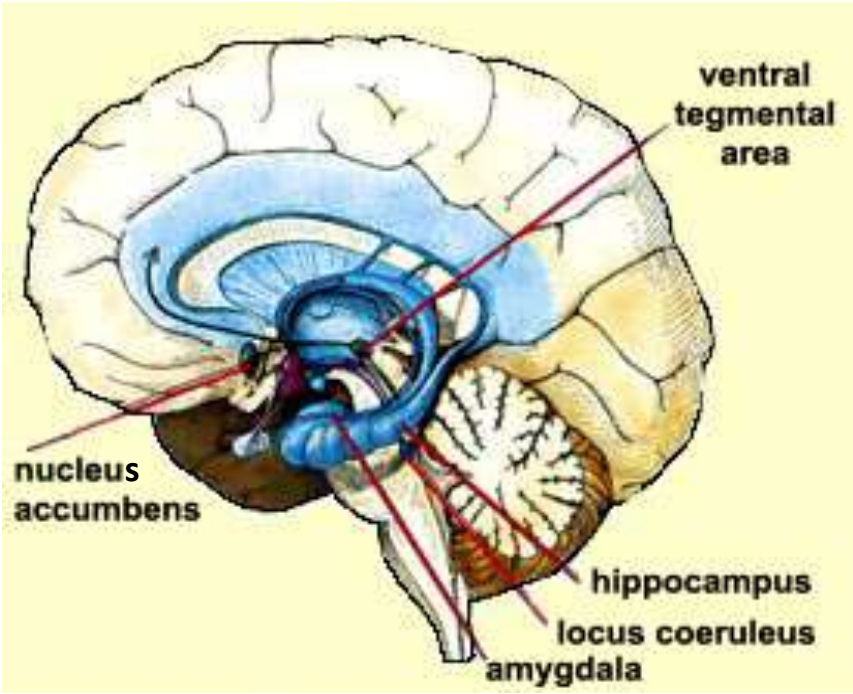
# Receptors

- **CB2** peripheral - immune modulating cells and microglia

- **CB1** neurological – **prefrontal cortex, amygdala**, **ventral tegmental area**, **nucleus accumbens**, cortex, hippocampus, BG, hypothalamus, cerebellum, spinal cord, peripheral neurons, DRG, C-fiber terminals;

# DA reward system

- A stimulus is encountered and deemed pleasurable; the cortex signals **VTA** to release DA into the **amygdala**, **PFC** and **NAc**. These deliver a sense of pleasure and focus the attention of the individual in order to learn and remember to repeat the behavior.



# Endocannabinoid binding

- **AEA** - **CB1**, weak **CB2**
- **2 AG – CB1 and CB2**
- (+ interact with opioid, serotonin, GABA, etc)

Effects: anti-inflammatory and neuropathic pain relief; affect working memory, mood, motivation and pleasure, alter feeding behavior, analgesic effects with exercise

(dark chocolate: N-acylethanolamines)

# Phytocannabinoid binding

- **THC**: **CB1** – psychoactive, general decrease in excitability except in DA reward system

- **CBD**: **not CB1 or 2**; multi-target agent, dose dep effects. Suppresses enzymes that metabolize AEA; stimulates 2 AG release; binds TRPV-1 (vanilloid) receptor; activates 5HT1A serotonin receptors; (etc – GPR55, adenosine, glycine, TRPA1…)

# Effects of Marijuana

- Rapid smoked vs 30 -60 mins orally
- Approx. 59% absorbed vs 3% orally
- 3-4 hour duration smoked, longer oral.
- Fat soluble - effects may persist or recur over 24 hrs. ?cumulative effect with recurrent use.

# Marijuana effects – short term

- Increased HR
- Increased BP
- Blood shot eyes
- Dry mouth and throat
- Cough
- Increased appetite
- Change in body temp
- Decreased vision
- Decreased eye pressure
- Relaxation
- Decreased attention span
- Slowed reaction times
- Decreased coordination and balance
- Anxiety
- Paranoia
- Disorientation
- Distorted sensations and perception
- Hallucinations

# Marijuana effects - long term?

- Respiratory effects: bronchitis, asthma, emphysema lung injury, cancers
- Immune system suppression
- Chromosomal/DNA injury
- Menstrual irregularity, decrease in sperm production, fertility and sex drive
- Hypertension and heart disease
- Tolerance
- Psychological dependence
- Long term memory loss
- Amotivational syndrome
- Aggression and hostility
- Delusions, panic, paranoia
- Psychoses
- Social/financial impact
- Poor neurocognitive and executive function

# Effects on The Developing Brain

- Fetal/neonatal exposure: limited data
- Childhood
- Adolescence/puberty: a particularly vulnerable developmental period when exposure to cannabinoids can cause lasting, region specific changes in the brain.

# Effects in Adolescence

- **Animals**: anatomical, physiological, behavioral

- **Humans**:

    1. NAc and amygdala gray matter abnormalities on MRI.
    2. Altered processing on fMRI.
    3. Psychiatry literature – multiple risks.
    4. Neurocognitive function.

# Marijuana Effects-adolescence

(Meier et al, PNAS, August 2012)

- 1037 subjects, neuropsych testing at 13 yrs- pre-THC exposure, interviews at 18, 21, 26, 32, 38 yrs and re-test at 38 yrs. (weekly use/dependence before 18 yrs)

**1**. Early persistent use leads to decline of IQ points (avg. 8) and measures of learning, memory, executive function and processing speed. *Deficits are apparent to others.*

**2**. Stopping use after age 18 yrs did not reverse effect.

**3.** Linear association – the more you use the more you lose;

# Medical cannabinoids

- Marijuana
- Sativex (nabiximols) - 1:1 CBD/THC spray. MS spasticity and pain in Canada, Europe, NZ
- Marinol (**dronabinol**) –synthetic THC. FDA approved antiemetic in chemo. Appetite stimulant with AIDS.
- Cesamet (**nabilone**) –synthetic THC analogue. FDA approved antiemetic in chemo.
- Other oral cannabinoid extracts
- Synthetic oral CBD preparations

# Potential Medical Uses

- Glaucoma*
- AIDS/HIV* - anorexia/cachexia
- Cancer* – **chemo related nausea**, cachexia
- Pain*- **HIV neuropathy, cancer related, MS**
- **Spasticity/spasms** – **MS***
- **Epilepsy***
- **Movement disorders** – tics, Tourette, chorea, dyskinesia, dystonia, tremor
- **Behavior/Sleep/Mood/Psychosis/Addiction**
- **(ALS, Hep C, Crohn's, agitation in alzheimers)***
- **Etc …**

# Epilepsy – animal data

- **THC**: benefit in some TLE/gen szr models, but pro-convulsant in rabbits and dog epilepsy models; high dose provokes vertical jumping in rats (?myoclonic); prolonged exposure in rodents (> 6mos) can lead to seizures

- **CBD** (CBDV): *not* pro-convulsant; effective in multiple acute szr models (gen, TLE, partial); not in chronic models of epilepsy

# Epilepsy - anecdotal

- -1990's: case reports + surveys : **1)** if low pre-drug baseline, sz frequency/intensity may increase; if high baseline – may decrease. **2)** seizure exacerbation in long term users after d/c use -? withdrawal or anticonvulsant

- 2001 – US survey of epileptic cannabis users -7% benefit, 2% worse, 90% no relation

- 2004 – Canada survey – 54% less freq, 68 % less severe

# Epilepsy

(Gloss and Vickrey, Cochrane review, 2012)

- 4 randomized trials, 48 pts, CBD 200-300 mg q day, low quality studies.

- **No reliable conclusions about efficacy**.

# Pediatric Epilepsy

(Porter and Jacobson, Epilepsy & Behav, 2013)

- Survey of Facebook parent group that shares information about using CBD-rich cannabis to treat their child's seizures
- 19 responders –
- 13 Dravet, 6 other intractable epilepsy

# Pediatric Epilepsy cont…

- 16 (84%) with reduced seizure frequency, 2(11%) no szrs
- Negatives: drowsiness, fatigue

- **Conclusion:** parents are using CBD in their children with treatment-resistant epilepsy

# Cannabinoids for Pediatric Epilepsy

- CBD pharmacologic preps have orphan drug status for Dravet syndrome.

- 2014 - FDA approved two trials of CBD prep. for intractable epilepsy in childhood.

  - Study dose tolerability and safety in open label trial with labs and EEG. (szr freq)

  - Goal: identify optimal dose to carry into placebo-controlled efficacy trials.

# Challenges to study

- Schedule I drug
- Dosing and formulations vary
- Placebo effect
- Blinding is difficult
- Unreliable measures
- Comparative data
- Drug-drug interactions
- Safety concerns (esp. in young)