Cannabis and Health

Module 12: Neurocognitive/Brain Disorders Part II

Lecture 6: Recent Research on Cannabinoids, Parkinson's Disease, and Alzheimer's Disease

CBD: The ideal drug for PD?

- Since the NAS Report, a recent invited review article provided evidence to the question
  - Is cannabidiol the ideal drug to treat non-motor Parkinson's disease symptoms?

- The paper reviewed preclinical and clinical studies specifically on CBD and PD
  - The review covered 7 preclinical models of PD using CBD, with six studies showing a neuroprotective effect of CBD
  - Further, across three three clinical trials, CBD was well tolerated, and all reported therapeutic effects in **non-motor symptoms** (psychosis, REM sleep, daily activities, stigma)

Crippa et al., 2019

CBD: The ideal drug for PD?

- Broadly, pre-clinical and clinical studies suggest positive effect of CBD on movement disorders
  - Dystonia
  - Huntington's Disease
  - Parkinson's Disease
- CBD has multiple CNS actions that may benefit non-motor symptoms in PD patients (mood, sleep, etc.)
- CBD is well-tolerated in PD patients

Crippa et al., 2019

CBD & The Endocannabinoid System: Treating PD

- The endocannabinoids system is involved in brain areas that process/execute body movements (basal ganglia)
  - Early PD: CB1r is downregulated
  - Later PD: CB1r and CB2r are upregulated
- Modulation of the endocannabinoid system can regulate neurochemical changes caused by reduced DA
- Preclinical studies indicate that CB1r agonists and drugs modulating endocannabinoid metabolism have a potential medicinal use in PD, with various proposed mechanisms
  - Anti-inflammatory effects
  - Inhibiting anandamide (endocannabinoid) hydrolysis

Crippa et al., 2019

Non-motor Symptoms of PD: CBD & Psychosis

- 1 in 3 PD patients experience psychosis in later stages
  - Unclear if it follows a similar path as standard PD.
  - Anti-PD meds increase DA (risk factor for psychosis)
  - Treatment is especially challenging… involves reducing medications for PD symptoms, or traditional antipsychotic meds (worsens PD symptoms)
- Evidence suggests that CBD has antipsychotic effects.
  - One open label study found CBD (150-400mg for 4 weeks) reduced psychotic symptoms, increased functioning, and was well tolerated
- Mechanisms are poorly understood, but may involve endocannabinoid system

Crippa et al., 2019

Non-motor Symptoms of PD: CBD & Anxiety/Depression

- The most common psychiatric symptoms in PD are anxiety and depression (~40%)
  - May be a result of altered mood circuits involving GABA, glutamate, and serotonin (due to DA neurotoxicity)
  - Low efficacy of traditional medications for these problems, and unintended effects include aggravated motor symptoms
- As discussed in earlier lectures, CBD may hold promise for anxiety/depression
  - Only very small trials have examined CBD
  - No clinical studies have actually examined CBD for depression in PD

Crippa et al., 2019

Non-motor Symptoms of PD: CBD & Sleep

- PD patients have increased sleep disturbances
  - Reduced quality of sleep, insomnia, restless legs syndrome, and REM sleep behavior disorder
  - Unclear why this occurs, it may involve DA neurotoxicity and related neurochemical alterations
- Traditional sleep medications are problematic for PD
  - Benzodiazepines may cause impaired motor coordination, which may worsen sleep problems in PD
  - Cholinesterase Inh. may cause GI disturbance, bradycardia
- CBD may be effective
  - A very small (n = 4) study found improved REM sleep in PD, when treated with CBD (75 or 300 mg)

Crippa et al., 2019

Non-motor Symptoms of PD: CBD & Cognitive Functioning

- Cognitive dysfunction occurs in 40% of PD patients
  - Attention, information processing, verbal fluency, memory
  - Seem to be caused by DA neurotoxicity affecting acetylcholine and glutamate activity (esp. later in disease)
  - Typical meds are problematic in PD
- CBD's neuroprotective effects have been reported in animal models, including for PD
  - Mechanism of action is thought to be related to anti-inflammatory and antioxidant actions
  - Also, CBD can attenuate microglial activation in critical PD substrates

Crippa et al., 2019

Non-motor Symptoms of PD: CBD & Pain

- Pain typically occurs with PD (60-80%)
  - Cannot be explained by peripheral nervous system
  - CBD has known effects on pain relief, as discussed in earlier lectures
  - Notably, more efficacious than CBD for pain has been THC
  - The efficacy of THC for PD is limited
  - THC may adversely affect cognition and motor coordination
- As with many non-motor symptoms in PD, larger-scale studies are needed to understand if/how CBD (or THC) may help treat pain

Crippa et al., 2019

Non-motor Symptoms of PD: CBD Summary

PSYCHOSIS
- 5-HT1A
- TRPV1
- CB1 (inhibition of the reuptake and metabolism of anandamide)
- CB2?
- Antioxidant/anti-inflammatory
- Neuroprotective effects

MOTOR EFFECTS
- 5HT1A
- Antioxidant/anti-inflammatory (involving PPAR-gamma and CB2?)

ANXIETY AND DEPRESSION
- 5HT1A
- Antioxidant/anti-inflammatory
- Increase adult hippocampal neurogenesis (CB1, CB2)

COGNITIVE DECLINE
- 5HT1A
- Antioxidant/anti-inflammatory (involving PPAR-gamma and CB2?)
- Increase adult hippocampal neurogenesis (CB1, CB2)

PAIN
- CB1
- CB2
- Anti-inflammatory

DYSKINESIA
- Antioxidant/anti-inflammatory (involving PPAR-gamma and CB2?)

SLEEP DISORDERS
- ?

NEUROPROTECTION
- 5HT1A
- Antioxidant/anti-inflammatory (involving PPAR-gamma and CB2?)
- Increase hippocampal neurogenesis (CB1, CB2)

Crippa et al., 2019

Cannabis & Dementia: Treating Agitation

- Day/night rhythm disturbances and sundowning (confusion in late afternoon/night) are the number one cause of long-term hospitalization for dementia
  - Benzodiazepines and antipsychotics are sometimes used to treat, but have substantial side effects
- An open-label pilot study examined dronabinol for circadian and behavioral disturbances (n = 6)
- Compared to baseline, two-weeks of dronabinol led to:
  - Reduced nocturnal motor activity ($P=0.028$)
  - Improved neuropsychiatric functioning ($P=0.027$)
  - Improved agitation, aberrant motor, and nighttime behaviors ($P<0.05$)

Walther et al., 2006

Cannabis & Dementia: Treating Agitation

- Subsequent studies of THC in dementia patients have found it to be generally well-tolerated

- Despite the initial promise of THC, it is rarely approved or used for agitation in dementia patients
  - Of 24 states/localities with legal medical marijuana, dementia is a qualifying condition in 10 (41.7%)
  - In the 5 states where information was available regarding qualifying conditions dementia was the indication for <0.5%

Ahmed et al., 2015; Maust et al., 2016;

Clinical Trial with Sativex

- Important to note that none of the studies examined plant derived products, a combination of THC and CBD, or CBD alone
- Scientists in the UK are launching a trial of Sativex for AD
- https://www.alzheimersresearchuk.org/cannabis-based-medicine-to-be-tested-in-alzheimers/
- They are specifically interested in whether Sativex may be helpful in terms of agitation
- One limitation is that they are only testing one ration of THC to CBD

Conclusions

- Scientists have theorized that CBD may be useful for PD although there is not a lot of research yet
- Scientists have also suggested that cannabinoids may be useful for some aspects of AD, although there is not evidence yet
- A new trial of Sativex will provide evidence regarding AD (although CBD is not being tested)
- Work here in CO on CBD and PD will be helpful

Discussion Prompts

- What ratio of CBD to THC would you recommend for study on PD?

- What ratio of CBD to THC would you recommend for study on AD?