Update on marijuana and cannabinoid compounds: Pharmacology, new pharmaceutical products and the latest legislation

Shanna Babalonis, Ph.D.
University of Kentucky
College of Medicine
Department of Behavioral Science
Center on Drug and Alcohol Research
Outline

- Background on cannabinoids (chemicals in marijuana)

- Current medications containing cannabinoids

- Discuss cannabidiol and its treatment potential

- Marijuana in the United States – potency and changing make-up of cannabinoids

- Trial at University of Kentucky examining cannabidiol as a potential treatment for marijuana abuse

- Conclusions
Phytocannabinoids

- There are approximately 500 phytochemicals that naturally occur in the marijuana plant
- Approximately 70 of these are unique to the marijuana plant and are called cannabinoids or phytocannabinoids
- Present in the plant’s buds, leaves, stalks, and seeds
- There are several classes of plant-derived cannabinoids, including:
  - $\Delta^9$ tetrahydrocannabinol (THC, THCV)
  - cannabinol (CBN), cannabindiol (CBDL)
  - cannabidiol (CBD, CBDV)
  - cannabichromenes (CBC)
  - cannabigerols (CBG)
  - Others: CBL, CBE, CBT
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Psychoactive effects

No known psychoactive effects
There are also endogenous cannabinoids produced in the body called endocannabinoids.

Examples: Anandamide, 2-AG

Endogenous ligands at the cannabinoid receptor

Present in both the CNS and periphery

Involved in regulation of sleep, memory, inflammation, immune functions, insulin sensitivity, fat and energy metabolism, reproduction (ovulation, implantation), expressed in breastmilk

THC and some other cannabinoids augment the action of endocannabinoids

Anandamide is degraded by FAAH (fatty acid amide hydrolase), 2-AG is degraded by MAGL (monoacylglycerol lipase) – naturally occurring enzymes

Isolated/synthesized endocannabinoids have never been administered to humans (exogenously – they would likely be degraded too quickly)
Cannabinoid Receptors

- Cannabinoids exert action at the primary cannabinoid receptors: CB$_1$ and CB$_2$

  **CB$_1$ receptor**  - the most abundant receptor in the CNS (basal ganglia, cerebellum, hippocampus, neocortex, spinal cord)
  - also located in the periphery (GI tract, cardiac tissue, reproductive system, fat tissue and skeletal muscle)

  **CB$_2$ receptor**  - primary located in the periphery, helps regulate immune function; present in GI tract
  - also present in the brain; less abundant than CB$_1$

- There are also strong indications that additional cannabinoid receptors may exist (e.g., GPR55)
Cannabinoid Agonists

Phytocannabinoids
THC - high affinity, partial agonist at CB$_1$
also exerts some partial agonist effects at CB$_2$

Cannabidiol (CBD) - mechanism at CB receptors not completely clear

Endocannabinoids
Anandamide - moderate affinity: full or partial agonists at CB$_1$
partial agonist at CB$_2$
2-AG - full agonist at CB$_1$ and CB$_2$

Synthetic Cannabinoid Chemicals
JWH compounds (K2, Spice) - synthetic, lab-made chemicals – do not occur in nature
- very high affinity, full agonist at both CB$_1$ and CB$_2$
Cannabidiol (CBD)

- Cannabidiol is present in the marijuana plant in varying levels (depending on the strain) and upon smoking, is absorbed into the lungs, entering the blood and brain.

- It is speculated to be a non-psychoactive component of marijuana.

- However, its mechanism of action at the CB receptors is not completely clear; some hypotheses:

  1) Increases availability of endocannabinoids through two mechanisms:
     - blocking auto-receptor binding or inhibiting uptake of endocannabinoids
     - increasing availability - through inactivation of FAAH and MAGL (enzymes that degrade endocannabinoids)
     - these mechanisms imply *indirect agonism* at CB\(_1\) and CB\(_2\) receptors
     - also suggests that CBD-induced endocannabinoid activity may interfere with THC/agonist binding

  2) CB\(_1\) antagonist and inverse agonist at CB\(_2\) receptors (unlikely)

  3) Others report little to no direct activity at CB\(_1\) and CB\(_2\) receptors.
CBD: Other Mechanisms

In cellular preparations and/or animal models CBD has displayed the following effects:

- Potent antioxidant, anti-inflammatory and neuroprotectant
  - antioxidant effects ≥ vitamin C and E in cellular models
  - mitochondrial, Ca$^+$ regulation

- Analgesic (antinociception, antihyperalgesia)
  - thought to be mediated through action at glycine and transient receptor potential channels (TRPs): TRPV1, TRPV2, TRPA1, TRPM8
  - cannabinoid/endocannabinoid effects may also contribute to analgesia

- Anticonvulsant (several models of seizure)
  - does not appear to be mediated by activity at CB receptors

- Other activity:
  - acts as 5HT$_{1A}$ agonist (antidepressant, antiemetic, anxiolytic, attenuates catalepsy)
  - modulates adenosine A2A signaling (also anti-inflammatory)
Preliminary Evidence: Therapeutic Effects of CBD

Cellular, animal, or small scale human studies have been conducted to show some therapeutic benefit of CBD; although no controlled clinical trials have been conducted:

- Huntington’s Disease
- Parkinson’s Disease
- Schizophrenia
- Anxiety
- Oxidative Injury
- Head Trauma
- Tumor/Cancer Treatment
CBD: Signals for Efficacy?

Multiple Sclerosis - combination THC/CBD medication approved in several European countries, Australia and Canada
- Phase 3 U.S. Trial scheduled to start this year

Cancer Pain: 3 Phase III trials in progress (THC/CBD)

Neuropathic Pain: Phase II trials in progress (THC/CBD)
Cannabidiol – Seizure Disorder

- Currently receiving quite a bit of attention, in part due to Dr. Sanjay Gupta’s CNN documentary, “Weed” and the Stanley Brothers in Colorado

- Highlighted CBD as a treatment for intractable seizure disorders (i.e., Dravet Syndrome, Lennox Gastaut)

- There are many preclinical research studies that indicate CBD has antiepileptic effects and some limited clinical studies; however the exact mechanisms of the anticonvulsant effects are unclear

- However, to date there have been no controlled clinical trials that examine its efficacy in adults or children

- The safety of long-term dosing is unknown

- Strains of marijuana with very high CBD content and low THC content (e.g., Charlotte's Web) are being administered to children in Colorado (and elsewhere)
Controlled Substances – Scheduling

All marijuana plant material, oils and resins are currently Schedule I under the US Controlled Substances Act.

Schedule I includes non-pharmaceutical cannabidiol oil and plants with high CBD content (however, some CBD enthusiasts are working through a regulatory loop-hole right now)

Medications containing cannabinoids need to be reviewed by the FDA (e.g., safety, abuse liability). There are two examples of cannabinoid based drugs that have gone through this process in the United States:

Marinol (dronabinol) = Schedule III
Cesamet (nabilone) = Schedule II
Pharmaceutical Products Containing Cannabinoids

- **Marinol** (dronabinol)
  - oral medication
  - synthetic THC
  - schedule III in U.S.
  - marketed for the treatment nausea/vomiting (chemotherapy);
    appetite stimulant (AIDS)
  - available in 2.5, 5 or 10 mg capsules

- **Cesamet** (nabilone)
  - oral medication
  - schedule II in U.S.
  - analog of dronabinol
  - marketed for the treatment of nausea/vomiting (chemotherapy)
  - available in 1 mg capsules
Pharmaceutical Products Containing Cannabinoids

Sativex (50-50 ratio of CBD: THC)
- buccal spray
- not currently available in the US
- approved in several countries for MS; in Canada for MS, intractable cancer pain
- manufactured by GW Pharmaceuticals
- 2.7 mg THC, 2.5 mg CBD per spray
- patients titrate up to about 10-15 sprays/day
- for comparison: 0.5 g marijuana = 50 mg of THC = 1 large joint
Pharmaceutical Products Containing Cannabinoids

Epidiolex (cannabidiol)
- in development by GW Pharmaceuticals
- CBD-only (98% CBD, trace cannabinoids, no THC)
- oral solution (bottle of liquid with syringe dropper)
- Treatment INDs have been issued for treatment of pediatric seizure disorder, sites are currently treating patients
- doses: 25 mg/mL and 100 mg/mL

Other drugs in GW’s pipeline:

CBDV (cannabidivarin – analog of CBD)
- in development by GW Pharmaceuticals (GWP42006) for epilepsy
- CBDV only
- Phase I trial to start in 2014 in United Kingdom

THCV – psychoactive, similar to THC - in trials for anti-obesity/drug for metabolic syndrome
Pharmaceutical Products Containing Cannabinoids

Under development:

Arvisol – controlled release cannabidiol
- Phase I trials for schizophrenia
- Echo Pharmaceuticals, Netherlands

- NIH-supported study in Germany is conducting a 3-arm trial to examine Arvisol, intranasal insulin and URB597 (FAAH inhibitor) for the treatment of schizophrenia
Pharmaceutical Products Containing Cannabinoids

- 3 other cannabinoid-based chemicals being tested by GW for:
  - Glioma
  - Neonatal Hypoxic-Ischemic Encephalopathy
  - Type II Diabetes
  - Ulcerative Colitis
  - Schizophrenia

Clinicaltrials.gov

45 studies involve cannabidiol (almost all very recent)

**Oral CBD:**
- Schizophrenia (200 mg) ➣ ANA=','%SCH
- Antipsychosis (600 mg)
- GVHD (Graft versus host disease) – anti-inflammatory
  - immunosuppressive effects (10-600 mg)
- Fatty Liver Disease (200 – 800 mg)
- Cue-Induced Opioid Craving (200 – 800 mg)
- Opioid Craving/Relapse (400-800 mg)
- Treatment for Marijuana Dependence (200-800 mg)
  - (FAAH-inhibitors also under investigation)

**SL Solution:**
- Inflammatory Bowel Disease/Crohn’s Disease/Ulcerative Colitis (5mg/BID)
Clinicaltrials.gov

THC and CBD:
Cancer Pain
Neuroprotection in Huntington’s Disease
Cognitive Dysfunction in Schizophrenia
Bipolar Disorder
Mucositis
THC-related Cognitive Function
Marijuana Dependence
Glioblastoma
Spasticity in children with cerebral palsy
Multiple Sclerosis – spasticity, neuropathic pain, detrusor overactivity
Intractable Cancer Pain
Spinal Cord Injury
States Allowing Recreational Marijuana

Colorado, Washington, Oregon, Alaska and Washington D.C. have legalized/decriminalized marijuana for non-medical purposes (adults 21 years and older)

Colorado and Washington: marketplace/store fronts
high concentration THC oil legal

Oregon and Alaska: no marketplace yet – both in development? no decision on oils?

Washington, D.C.: mayor is allowing it, even though there is congressional opposition

Projected: California (and others) in 2016

DUI Laws: Blood levels below 5 ng/mL (3-5 hrs after smoking; “edibles” (marijuana-infused food) will take longer).
THC Content Increasing

High THC content marijuana is now widely available in street marijuana, medicinal marijuana and legalized recreational marijuana.

Mean THC content of marijuana in the US:

- 1970s: 1 - 2%
- 1990s: 3 - 4%
- 2010s: 10 - 15%
- Medical marijuana: 10 - 20%
- Legal recreational marijuana: 15 - 20%+
- THC oils: 50-80%+
THC Content Over Last 20 Years

Mean THC concentration (%)

Year


15
10
5
CBD Content Decreasing

As THC content is increasing, CBD content is decreasing (through selective breeding, growing techniques); increases sales

Recent paper in PLoS One:
Analyzed 206 marijuana samples confiscated from recreational users and growing operations in Australia

Recreational Users:
Mean THC content: 14.9%
Mean CBD content: 0.14%

Indoor Growing Operations:
Mean THC content: 19.6%
Mean CBD content: 0.14%

Marijuana purchased in Washington
CBD Reduces Risk of THC?

Many in the scientific community and lay press indicate that CBD reduces the high and psychoactive effects of marijuana; also reduces anxiety/paranoia.

However, there is relatively weak evidence that CBD may protect against the adverse effects produced by THC.

- Animal studies have provided mixed results.

- Several small *correlational* studies have associated high THC, Low CBD marijuana with increased anxiety and a younger age of onset of first psychotic episode.
Multisite Trial: Cannabidiol Effects on Smoked Marijuana

- There have been a few studies that have suggested that CBD can decrease the euphoric, anxiogenic and motor impairing effects of marijuana.

- However, these studies are case studies or do not provide well-controlled data.

- The National Institute on Drug Abuse (NIDA) funded a 3-site trial that examines oral CBD alone and in combination with smoked marijuana.

- Sites include: University of Kentucky, Columbia University, Medical University of South Carolina.
## Methods

### Participants
- Healthy adults, ages 18 – 50
- Frequent marijuana smokers (4x per week)
- Not seeking treatment for marijuana use

### Study Design
- 8 week outpatient study
- 1 session per week (due to CBD half-life)
- Conducted at Robert Straus Behavioral Science Building on UK Campus
- All FDA, DEA, IRB and human subjects permissions obtained
**Methods**

**Drugs:**
- Oral cannabidiol: 0, 200, 400, 800 mg
- Smoked marijuana: 0, 5.6% THC

Each dose combination tested once
CBD administered 90 minutes prior to MJ

**Measures:**
- Subjective, psychomotor, physiological and cognitive assessments are collected at regular intervals (7.5 hrs)
- Self-administration: participants can purchase additional puffs 2.5 hrs after sampling marijuana

**Objectives:**
1) Assess the safety and abuse liability of oral CBD alone
2) Determine CBD effects on the reinforcing, subjective, cognitive, and physiological effects of smoked marijuana
“I Feel High”

Inactive Marijuana

Active Marijuana

<table>
<thead>
<tr>
<th>CBD (mg)</th>
<th>0</th>
<th>200</th>
<th>400</th>
<th>800</th>
</tr>
</thead>
</table>

Time

mm (max = 100)
“I Like the Marijuana”
“The Marijuana is Strong”

Inactive Marijuana

Active Marijuana

CBD (mg):
- 0
- 200
- 400
- 800

Time

mm (max = 100)

0 30 60 90 120

0 30 60 90 120

MJ

MJ
Study Conclusions

1) Oral CBD is a safe medication in a tolerant population in the dose range tested (up to 800 mg)

2) CBD does not display abuse liability in a marijuana-abusing population

3) CBD was placebo-like on all measures tested and there was no signal for CBD to decrease marijuana subjective effects

4) In this acute interaction study, there was no signal for CBD as a treatment for marijuana abuse
Summary

- THC content in marijuana is increasing (12 fold increase since 1970s); however, it does not appear that CBD, even at relatively high doses, decreases the positive or aversive drug effects of marijuana

- There is preclinical evidence indicating that cannabidiol acts as an antioxidant, anti-inflammatory, neuroprotectant and anticonvulsive; however, there have been no controlled trials demonstrating efficacy in humans

- Clinical trials are underway for numerous indications; treatment INDs have been issued for pharmaceutical-grade cannabidiol oil for the treatment of pediatric seizure disorders

- Acute doses of cannabidiol appear to be well-tolerated in several patient groups (e.g., Huntington’s Disease, Schizophrenia)

- However, the long term safety of cannabidiol has not been established; given that cannabinoid receptors are ubiquitous in the brain and periphery (particularly in cardiac tissue, reproductive system, GI tract), this needs to be carefully examined