Cannabis and Anxiety: A Clinician's Dilemma

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Financial Disclosure Statements

◊ **The Planning Committee:** George Keepers, Bill Wilson, Micaela Sandoval, Sean Stanley, and Kevin Howden have **no financial conflicts to disclose.**

◊ **The Presenters:** Neisha D’Souza, Sean Stanley, Jeramy Peters, and Eric Weathers have **no financial conflicts to disclose.**
Learning Objectives

- Describe cannabis and the endocannabinoid system
- Identify indications and contraindications of cannabis use
- Analyze current research relating to cannabis use in the management of anxiety
- Identify your own assumptions regarding how cannabis may facilitate or hinder one’s recovery
- Demonstrate how to have an informed discussion about cannabis with clients/patients
The Cannabis Flower
The Basics of Cannabis

- Order: Rosales
- Family: Cannabaceae
- Genus: Cannabis
- Species
  - Cannabis sativa
    - Northern China/Mongolia/ Russia and Europe
    - Photoperiod flowering
  - Cannabis indica
    - India, most of Asia, the middle east and Africa
    - Photoperiod flowering
  - Cannabis ruderalis
    - Eastern Europe, Russia
    - Autoflowering
Major Compounds Found in Cannabis

✧ **Cannabinoids**

✧ > 60 identified

✧ Main active component of cannabis plant

✧ Most frequently studied (THC, CBD)

✧ **Terpenes**

✧ > 100 isolated from cannabis

✧ Distinct smell, beta-caryophyllene is what drug dogs are trained to identify

✧ “Fingerprint”, distinguish strains (Indica vs. Sativa) and grow sites
Strains: Indica? Sativa?

- No consensus about phenotypical differences.\(^2^0\)
- Due to selectively breeding clear distinctions are not apparent.\(^2^1\)
- Studies have shown that cannabis constituents, primarily terpenes, can be used to distinguish between indica and sativa plants.\(^2^0,2^1\)
- \textbf{IF} there is a non-placebo difference between strain effects it is likely due to unique terpene profiles (and cannabinoid content to a lesser extent).\(^2^0,2^1,2^2\)
What do people say?

Indica

“relaxing”
“couchlock”
“body high”
“increased sense of calm”
“sedating”

Sativa

“uplifting”
“energetic”
“cerebral”
“increased wellbeing”
“good for daytime smoking”
Delta-9-tetrahydrocannabinol (THC)

- Psychoactive, responsible for the “high”
- Highly lipophilic
- Partial CB1 and CB2 agonist\(^{11,15,24}\)
- Metabolized by CYP450 enzymes, \( (CYP2C9)\)^{25,75}
- Eliminated in urine and feces
- Drug tests detect THC-COOH metabolite
Cannabidiol (CBD)

- Does not cause “high”\(^{27}\)
- CB1 and CB2 inverse agonist
- Metabolized by CYP450 enzymes (CYP3A4, CYP2C19)\(^{26}\)
- Tempers the effects of THC
  - Possibly by blocking THC conversion to the more psychoactive 11-hydroxy-THC by cytochrome P450 3A11\(^{15}\)
The Endocannabinoid System

Adapted from Figure 1. The endocannabinoid System in the Nervous system as presented in "Information for health care professionals cannabis and the cannabinoids"
Endogenous Endocannabinoids

**Amides**
- arachidonic acid and ethanolamide
- retrograde neurotransmitter
- Anandamide (AEA)
  - Sanskrit for Eternal Bliss
  - Agonist at CB receptors
  - Higher affinity for CB1 vs CB2
  - Bind TRPV1 (vanilloid) receptors

**Glycerol Esters**
- 2-arachidonoylglycerol (2-AG)
- retrograde neurotransmitter
- Greater potency/efficacy relative to anandamide
The Endocannabinoid System: **CB₁** receptor

- Primarily found in the **brain** and **nervous system**.³,⁴,⁵
The Endocannabinoid System: **CB2** receptor

- Primarily found in **immune system tissue**
  - Spleen, tonsils, thymus gland, and on leukocytes
  - Found on the **microglial cells** of the brain
- Has significant immune modulating (suppressive) effects
  - Likely modulate cytokine release
- Upregulated in many pathological conditions
The Endocannabinoid System: Enzymes

- Production\textsuperscript{2}
  - phosphoglycerides
- Transportation
  - intracellular calcium causes endocannabinoid release
  - Theoretically an undiscovered transport protein may exist
- Degradation\textsuperscript{2,9}
  - Fatty acid amide hydrolase (FAAH)\textsuperscript{9,10}
  - Monoacylglycerol lipase
**Cannabinoid Pharmaceuticals**

**Dronabinol tablet (MARINOL) Schedule III**

**Dronabinol liquid (SYNDROS) Schedule II**

- synthetic delta-9-tetrahydrocannabinol
- FDA approved:
  - nausea and vomiting a/w chemotherapy
  - Anorexia and weight loss a/w AIDS

**Nabilone (CESAMET) Schedule II**

- THC analog
- FDA approved:
  - nausea and vomiting a/w chemotherapy

**Nabiximol (SATIVEX) sublingual spray**

- Whole cannabis extract
- Each spray delivers a dose of ~2.7 mg THC and 2.5 mg CBD.
- Approved in Europe and Canada for MS related spasticity and cancer pain
- Currently in phase three trials in the US for cancer pain
Cannabis and Clinical Studies

Photo: http://www.huffingtonpost.ca/2014/05/22/medical-marijuana-clinical-trial-canada_n_5373658.html
## Herbal Cannabis

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<td>HIV(^{32,59,69})</td>
<td>Alzheimer’s(^{45,46,47,48})</td>
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## Benefits may Outweigh Risks
- Palliative Care\(^{41,42,43}\)
- Chemo related nausea/vomiting\(^{59}\)
- Cachexia\(^{11,15}\)
- Multiple Sclerosis\(^{44}\)
- Chronic pain\(^{40,59,70,71}\)
- Neuropathic pain\(^{44,59}\)
- Rheumatoid Arthritis\(^{39,59,67}\)
- Glaucoma\(^{11,15}\)
- Alzheimer’s\(^{45,46,47,48}\)
- IBS\(^{64}\)
- Crohn’s\(^{11,15}\)
- Ulcerative Colitis\(^{11,15}\)

## Unclear Role
- Anorexia Nervosa\(^{15}\)
- ALS\(^{11,15}\)
- Epilepsy\(^{59}\)
- Migraine\(^{64}\)
- Fibromyalgia\(^{64}\)
- Dystonia\(^{44}\)
- Sleep Disorders\(^{11,15}\)
- PTSD\(^{57,58,65,66}\)
- Depression\(^{38,58,59,65,68}\)
- Anxiety\(^{3,8,24,27,31,35,54,58,59}\)
- Addiction\(^{49,59}\)

## Risks may Outweigh Benefits
- Post operative pain\(^{11,15}\)
- Osteoporosis\(^{11}\)
- Huntington’s\(^{11}\)
- Parkinson’s\(^{11}\)
- Tourette’s\(^{11}\)
- Asthma\(^{59}\)
- As a chemotherapy\(^{11,15}\)
- Schizophrenia\(^{63}\)
- Acute pain\(^{44}\)
## Benefits may Outweigh Risks
- Multiple Sclerosis
- Chronic pain
- Neuropathic pain
- Rheumatoid Arthritis
- Glaucoma
- Alzheimer’s
- IBS
- Crohn’s
- Ulcerative Colitis
- Anxiety
- Depression
- Schizophrenia
- Addiction
- Epilepsy
- Palliative Care

## Unclear Role
- Anorexia Nervosa
- ALS
- Acute pain
- Migraine
- Fibromyalgia
- Dystonia
- Sleep Disorders
- Chemo related nausea and vomiting
- Palliative Care
- Cachexia
- PTSD

## Risks may Outweigh Benefits
- Post operative pain
- Osteoporosis
- Tourette’s
- Asthma
- As a chemotherapy
Works Cited


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Works Cited


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The Evidence: Cannabinoids and Anxiety

“Cannabis helps with my anxiety.”

Photo credit: http://www.huffingtonpost.com/2013/12/20/kinds-of-psychotherapy-try_n_4466536.html
Motives for Cannabis Use

- Subjective reduction of anxiety is a commonly reported motivation for use
  - Adolescents: novelty seeking
  - Young adults: reduction of anxiety
  - Middle age: insomnia
  - Older adults: health conditions (e.g. chronic pain, cancer, glaucoma)
Nabilone (CESAMET)
Synthetic THC, \( CB1 \) partial agonist

- 1981 Study\(^3\)
  - 1.0-2.5 mg (low dose)
  - Statistically significant reduction in Hamilton Anxiety Scale scores

- 2015 Study\(^4\)
  - 0.5-2.0 mg (1 mg BID)
  - Greater benefit compared to placebo as secondary outcome in RCT for treatment of pain in fibromyalgia
Dronabinol (MARINOL)

THC, CB1 partial agonist

✧ OCD: 2008 case reports of improvement in two patients with refractory OCD at 10 mg two and three times daily, respectively\(^5\)

✧ Trichotillomania: study of 14 patients showed improvement on MGH-HPS with doses of 2.5-15 mg\(^6\)

✧ Greater benefit compared to placebo as secondary outcome in RCT of patients with chronic pain\(^4\)
Rimonabant (ACOMPLIA)\textsuperscript{7}

\textit{CB1 antagonist}

\diamond 2006: developed as a treatment for obesity and smoking cessation

\diamond 2008: withdrawn from the European market due to increases in anxiety, depression, and suicidality
Cannabidiol (CBD)

$5-HT_{1A}$ agonist and CBL inverse agonist

- 1974: early human study establishing block of the effects, including induction of an anxiety component, of THC by CBD$^8$
  - 30 mg THC
  - 15-60 mg CBD
Cannabidiol (CBD) in Social Anxiety Disorder

Social anxiety disorder:

- 2011: small parallel-group trial of patients with SAD
  - 600 mg
  - Greater improvement in anxiety factor compared to placebo on a public speaking test
  - Judged at high risk of bias in 2015 JAMA systematic review

- “There is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders.” (National Academy Report)
Modulation of the Endocannabinoid System

- AM404 - Anandamide (endocannabinoid) transport blocker
  - Elicited anxiolytic-like behaviors in rats in elevated plus maze
    (proxy test for anxiety)\textsuperscript{10}

- FAAH inhibition - Endocannabinoid hydrolytic enzyme
  - Blockade modulated anxiety in rats\textsuperscript{11}
Effects of WIN 55212-2 on % open time (a), absolute open time (b), % open arm entries (c), and number of total arm entries (d) during a 5-min exposure to the elevated-plus maze. *, p < 0.05; **, p < 0.01, significantly different from vehicle control.¹²

Sachin Patel, and Cecilia J. Hillard J Pharmacol Exp Ther 2006;318:304-311