Getting Into the Weed: Potentials and Pitfalls Affecting Medical Use

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Objectives

- Describe in simple terms the endocannabinoid system and which body systems are most affected by it
- Differentiate the effects of THC and CBD and the physical and psychoactive roles they play
- Describe major differences in effects between common dosage forms of cannabis or cannabinoid medicines
- Describe common adverse effects and the populations at greatest risk for severe harm from cannabis use
- *Use knowledge to aid in decision-making and risk-analysis when considering medical use recommendations for individuals or populations*

2

Which is medicinal cannabis?

Herbal/Botanical Medicine	Drug
• Complex, many "active" ingredients	• Single "active" ingredient (products can combine two or more drugs)
• May have highly variable content of ingredients in each batch	• Has generally consistent content of ingredients in each batch
• Used in raw plant form or extracts	• Often available in a limited number of dosage forms
• Often available in many dosage forms	• Dosage range generally defined
• Dosage range may vary widely	

3

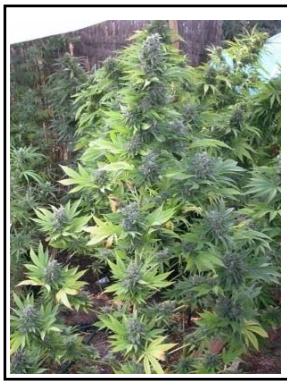
The Definitions….

- **Cannabinoids:** a group of related chemicals from the *Cannabis sativa* plant that act on/with cannabinoid receptors
  - **Cannabimimetics:** synthetic chemicals that mimic actions of cannabinoids
  - **Phytocannabinoids:** chemicals from other plants that act on/with cannabinoid receptors
- **Endocannabinoids:** chemicals made internally that act on/with cannabinoid receptors in the body
- **Cannabinoid receptors:** receptors that are effected by cannabinoids, endocannabinoids, or other chemicals
- **Terpenes:** chemicals in *C. sativa* that provide the characteristic odors and also have pharmacologic activity

5

Think of cannabis as a chemical factory….

6



7

8

Kief: resin separated from the rest of the buds

Hashish: pressed kief

How can cannabis have medicinal use?

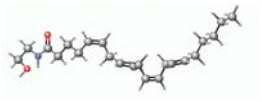
The endocannabinoid system

= endocannabinoids + endocannabinoid receptors

10

Endocannabinoids

- Multiple and more to discover!
  - anandamide (AEA)
  - 2-arachidonoylglycerol (2-AG)
  - palmitoylethanolamide (PEA)



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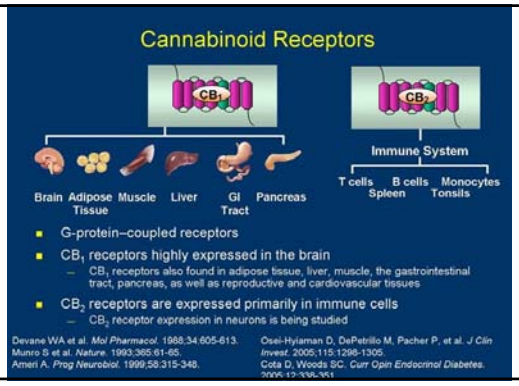
- Signaling chemicals
  - Involved in many functions
  - Generally VERY short-lived
  - Act on more than just the CB_1 and CB_2 receptors

11



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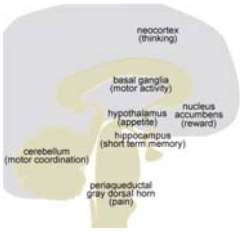
CB_1 and CB_2 Receptors

CB_1



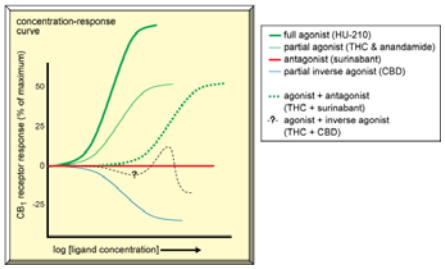
CB_2

- Immune system cells
  - Moderates movement of immune cells and signaling
- Microglia
  - Possible role in neurodegenerative disorders

Adapted from: Franson, KL. What is Known About the Clinical Pharmacology of Medical Cannabis? 5/2013.

13

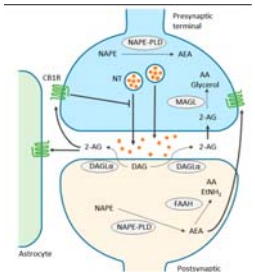
Receptor Activity



Borgelt LM, et al. *Pharmacotherapy.* 2013;33(2):195-209.

14

Neuronal and Cellular Signaling



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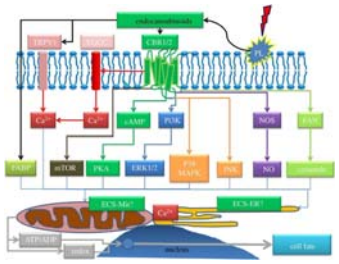
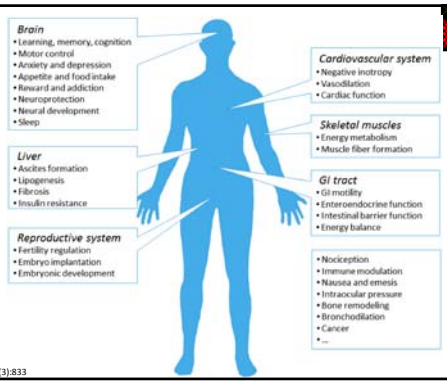


Nunn A, *et al. Phil Trans R Soc B.* 2012;367:3342-3352.

15

Endocannabinoid System Involvement



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16

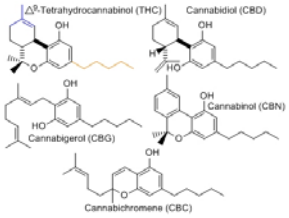
Describe in simple terms the endocannabinoid system and which body systems are most affected by it

- ✓Internal signaling/control/feedback system made up of endocannabinoids + cannabinoid and other receptors
- ✓Central and peripheral nervous system, the gut, and the immune system
  - Cardiovascular system

17

Cannabinoids from *C. sativa*

- **THC** (tetrahydrocannabinol)
- **THCV** (tetrahydrocannabivarin)
- **CBD** (cannabidiol)
- **CBN** (cannabinol – breakdown product)
- **CBC** (cannabichromene)
- **CBG** (cannabigerol)
- And on and on…..



18

Physiologic Effects

THC

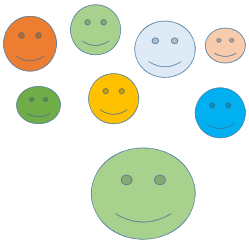
- Psychoactive
- CB_1R/CB_2R partial agonist
- Inhibitor of 5-HT3 receptors
- Some activity on other receptors
- Activities
  - Increased: vasodilation, somnolence, analgesia, intraocular pressure
  - Decreased: body temperature, cognition, memory, coordination, GI movement, inflammation

CBD

- Non-psychoactive*; ameliorates some THC adverse/psychoactive effects
- Enhances or modulates activity of AEA and other cannabinoids for CB_1R/CB_2R
  - Doesn't directly bind CB_1R/CB_2R
- Activities
  - Anticonvulsant, anxiolytic, antiemetic, neuroprotective, sleep-promoting, anti-inflammatory*

19

Entourage or Ensemble?



20

Terpene Components of Cannabis

- Essential oil components
- In foods; GRAS status in US
- Pharmacologic activity alone
- Synergistic with various cannabinoids
  - Modulate receptor activity

- **Limonene** (anxiolytic, immunostimulant, antimicrobial, apoptosis of breast cancer cells)

- **α-pinene** (acetylcholinesterase inhibitor, anti-inflammatory, bronchodilatory)

- **β-carophyllene** (anti-inflammatory, antimalarial, selective CB_2 agonist, gastric cytoprotective)

- **Linalool** (anti-anxiety, local anesthetic, analgesic via adenosine A_{2A}, anticonvulsant/anti-glutamate)

- **β-myrcene** (anti-inflammatory via PGE-2, sedating, muscle relaxant, hypnotic, blocks hepatic carcinogenesis by aflatoxin, analgesic antagonized by naloxone)

21

Differentiate effects of THC and CBD and their physical and psychoactive roles

	THC	CBD	THC+CBD	Terpenes
"high" or "intoxication"	✓			
Anticonvulsant activity		✓		✓
Pain relief	✓	✓	✓✓	✓
Decreased intraocular pressure	✓	✓?	✓	
Antiemetic activity	✓	✓	✓	
Anxiolytic		✓		✓
Cardiovascular effects (hypotension, tachycardia)	✓			
Sedation/somnolence	✓	✓?		✓

22

Differences in Dosage Forms

23

Inhalation - Classic …not classy

- Fastest absorption
- Fastest onset of action

- Exposes lungs to combustion products
- Risk of second-hand exposure to others

24

Boiling Points

Cannabinoid	°F	Terpenoids
CBC and THCV	428	
	388	Linalool
CBN	365	
CBD	356	
	350	Limolene
	330	Myrcene
	329	β-pinene
THC	315	
	313	α-pinene
	246	β-carophyllene
CBG (melting)	125	

25

Inhalation

The Volcano – used in many of the Israeli medical studies

Disposable CBD vape pen

Oral…

CC NAFMO

Medicinal **versus** **Primarily Recreational**

…and Oral

- For cannabis-naïve patients
  - less stigma
  - more like "medicine"
- Slower absorption
- More intra-patient variability in absorption and bioavailability

Sublingual/Buccal

- Recreational and medicinal products
- Mucosal absorption – directly into bloodstream, avoids first pass effect of liver metabolism
- Products are often a mix of mucosal and oral absorption

Topical

Homemade

Commercially available

30

Describe major differences in effects between common dosage forms of cannabis or cannabinoid medicines

Inhalation	Fastest onset of action – within minutes	When fast symptom relief is important, such as for pain Avoid first pass effect entirely
Oral	Slow onset of action – 1-2 hours Longer duration of action	For chronic symptoms Bioavailability affected by first pass metabolism More patient-to-patient variability
Sublingual/buccal	Faster absorption and onset than oral, but slower than inhalation	For chronic symptoms Some avoidance of first pass effect
Topical	For local action; some systemic absorption, but is much slower	When pain is localized and/or occasional and need to avoid systemic side effects

31

Adverse Effects and Risks of Cannabis Use

33

Adverse Effects – Short-Term

- **Many fairly well-known, primarily associated with THC component**
- **Variable severity, generally dose-related**
  - **Red eyes**
  - **↑ hunger**
  - **Dry mouth**
  - **Sedation, somnolence**
  - **↑ heart rate, hypotension/postural hypotension**
  - **Coughing, wheezing , increased mucus, dysphagia (smoked)**
  - **Mood changes, ↑/↓ anxiety, temporary paranoia/psychosis**
  - **↓/impaired reaction time, lack of coordination**
  - **Impaired cognition, altered time perception, memory loss**

34

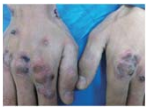
Adverse Effects – Long-Term

- Not as well-understood, may or may not be primarily associated with THC component
- Information primarily based on recreational users vs medicinal users
  - Psychological and physical dependence leading to addiction ➔ cannabis use disorder (CUD)
    - Addiction potential compared to other substances of abuse
    - New data - CBD may ease physical withdrawal symptoms
  - Worsening psych disorders, lethargy/apathy, depression/anxiety
  - Impaired cognition, memory loss
  - Decreased GI motility

35

Adverse Effects – Long-Term

- Allergies and skin reactions



- Cannabis/cannabinoid hyperemesis syndrome
  - Severe cyclic vomiting

- Lung cancer (smoked) ?
  - Basic science – both help and harm in cancer studies are documented
  - Thyroid and breast cancer more problematic
- ↓ immune response, ↓ sperm production ?

36

Adverse Effects - Populations

- **Pregnancy**
  - maternal use before and during ➔ increased risk of acute nonlymphoblastic leukemia (ANLL)
  - lower birthweight ?
  - ???

- **Adolescent use**
  - more likely to develop CUD
  - changes in brain development ➔ decreased IQ ?
  - earlier onset/increased schizophrenia ?

37

Adverse Drug Interactions

The great unknown….

38

Metabolism/Possible Drug Interactions

Cannabinoid	3A4	2C9	2C19	?
Δ9-THC	Substrate	Substrate		?
CBD	Substrate	Substrate	Substrate	?
CBN	Substrate	Substrate		?
?	?	?	?	?
?	?	?	?	?

39

Metabolism/Possible Drug Interactions

Cannabinoid	1A2	2D6	3A4	?
Δ9-THC	Inducer ↓ chlorpromazine, clozapine, olanzapine, cyclobenzaprine, haloperidol	-	-	?
CBD	-	Inhibitor ↑ SSRIs, tricyclics, opioids, beta-blockers, risperidone	Inhibitor ↑ haloperidol, CCBs, sildenafil	?
?	?	?	?	?

40

Drug Interaction Studies

Drug	Effect	Comments
Warfarin	Increased levels / INR	THC and CBD
Alcohol	May increase THC levels	
Theophylline	Decreased levels	Smoked
Indinavir/ nelfinavir	No effect	Smoked
Docetaxel/ irinotecan	No effect	Infusion
Clobazam	Increased clobazam	CBD in treated children
CNS depressants	Additive effects	EtOH, barbiturates, benzos
?	?	?

41

Describe common adverse effects and the populations at greatest risk for severe harm from cannabis use

- ✓**CNS, cardiovascular, psychiatric**
- ✓**Pregnant women, adolescents**
- ✓**People on drugs metabolized by the enzyme systems affected by cannabis**

42

Considerations for Therapeutic Use and/or Drug Development

43

Questions

- What is the most appropriate ingredient, or combination of ingredients, for each medical condition?
- What is the best dose?
- What is the best route of administration?
  - How does the route affect the bioavailability?
  - Is bioavailability affected differently for the different components?
- What about drug interactions?
- How does the treatment compare to standard treatment?
  - Both possible risks and possible benefits; NNT
- What **patient** factors affect the choice of treatment, dose, and route of administration?

44

A Game-Changer?

- **April 19th – public hearing by FDA on Epidiolex approval**
- **Late June – final decision**

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45

Questions and/or Follow-up

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47