What's the Tea on THC…and CBD, Dronabinol, Epidiolex (Cannabidiol)?

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Disclosures

I have no personal or financial conflicts of interest relating to this presentation

Any unlabeled/unapproved uses of drugs or products referenced will be disclosed

Objectives

1. **Differentiate types of THC, CBD, hybrids, and prescription formulations of marijuana**
2. **Evaluate potential therapeutic uses of each formulation of marijuana**
3. **Predict potential medication interactions, disease state interactions, and side effects of each formulation of marijuana**

FYI

This presentation covers products from dispensaries and pharmacies.

This presentation covers the main products, having the most data.

This presentation does not cover ‘street’ marijuana not purchased in a dispensary, as it is not regulated and may be contaminated or adulterated with anything.

Grown Cannabinoids

- *Cannabis Sativa, Cannabis Indica*
  - THC (Type I), CBD (Type III), Hybrid (Type II)

- Over 500 different compounds
  - Unknown how many compounds may have activity
  - Many being studied for pharmaceutical, medical and recreational use
    - Ruderalis, Terpenes, THCA, CBN, THCA, CBG

Medical vs Recreational vs Street Marijuana

a. Medical Marijuana: not taxed
b. Recreational marijuana: taxed
c. Street Marijuana
    I. Potential contaminants
    II. May be fentanyl and other substances with little, to no, marijuana
    III. Illegal

Potential Therapeutic Use THC

- Psychoactive form of THC
  - Sativa most common form
  - Used through virtually any route
  - Oral, inhaled, rectal, vaginal, transdermal
- Peak
  - Inhaled: usually within 30 minutes
  - Oral: 1 to 8 hours, depending on formulation
- Decrease: anxiety,
- Increase: euphoria, somnolence

Potential Side Effects THC

- Toxicity (more likely in children and oral products)
  - encephalopathy, coma, respiratory depression
  - Crosses placenta and appears in breastmilk
- Cardiovascular: incr/decr hr/bp
- CNS: somnolence, ataxia, slurred speech, paranoia/panic attack, tremor, ataxia, memory loss
- GI: xerostomia, incr appetite, n/v, hyperemesis
- Other: cancer, *Aspergillus* infection
- Not Federally regulated: see dronabinol for more

Potential Med Interactions THC

- THC in dispensaries not well studied
- See dronabinol
- Potentially all medications metabolized by CYP1A2, CYP3A4, CYP2C9
  - Examples: amiodarone, clozapine, clobazam, olanzapine, rifampin, theophylline, warfarin,

Potential Disease Interactions THC

- THC in dispensaries not well studied
- Cardiac: see side effects
- Pulmonary (inhaled thc): chronic inflammatory changes, cancer
- Cyclic vomiting: exacerbates

Potential Therapeutic Use CBD

- Nonpsychoactive:
  - Indica most common form used
- May decrease anxiety
- Pain
  - Acute pain: may have greatest benefit
  - Chronic pain: may not improve quality of life, pain intensity, physical function
- Poorly studied
  - If became FDA approved, may have better data

Potential Side Effects CBD

- CBD in dispensaries not well studied
- Hepatic toxicity
- See cannabidiol

Potential Med Interactions CBD

- CBD in dispensaries not well studied
- Medications metabolized by CYP3A4
  - Examples: tacrolimus
- See cannabidiol

Potential Disease Interactions CBD

- CBD in dispensaries not well studied
- See cannabidiol

Hybrid Marijuana

- Based on content of individual agents
  - Action: Content altered for desired effect
    - Higher THC content, higher cns action
    - Higher CBD content, less cns action
  - Side effects: THC and CBD meant to offset side effects
    - May have increased anxiety, paranoia, etc
    - May actually offset and decrease side effects
    - Poorly studied, hypothetical
  - Medication and Disease state interactions
    - Must monitor for THC and CBD d/t both being present

Synthetic Substances

- FDA Approved Medications
  - Data Show therapeutic use
  - Criteria required for FDA approval
  - NOT including synthetic illicit substances
- Dronabinol (Marinol, Syndros):
  - Synthetic delta-9 thc
  - Contains sesame oil
- Cannabidiol (Epidiolex)
- Nabilone (Cesamet)

Potential Therapeutic Uses Dronabinol

- **ALL potential uses: risk vs benefit**
- FDA approved antiemetic:
  - Cancer patients who failed other agents
  - Start 5 mg before/after chemo
- FDA approved increase appetite:
  - AIDs patients
  - Start 2.5 mg oral twice daily
- Other potential uses:
  - Off-label
  - Not recommended d/t lack of data

Potential Side Effects Dronabinol

- Similar side effects to THC, including 'high'
- Cardiac: orthostatic hypotension, incr/decr bp/hr,
- CNS: euphoria, paranoia/panic attack, exacerbate psychiatric disorders
- GI: paradoxical n/v, abd pain, diarrhea
- Other: vision changes.
  - Many other side effects listed in package insert, not be confirmed due to dronabinol

Potential Med Interactions Dronabinol

- Alcohol: increased CNS side effects
- CNS depressants: additive vs synergistic effect
- Potentially all metabolized via CYP2C9, CYP3A4
  - Examples: amiodarone, ketoconazole, macrolide abx, verapamil, warfarin

Potential Disease Interactions Dronabinol

- Cardiac disorders: d/t cardiac side effects
- Patients: Not recommended: nursing, pediatric, pregnancy. Caution in elderly
- Psychiatric: may exacerbate mania, depression, schizophrenia. May cause paranoia, panic attacks
- Seizure d/o: increase in seizures
- SUD: carries risk of abuse

Potential Therapeutic Use Cannabidiol

- Lennox-Gastaut Syndrome (LGS), Dravet Syndrome (DS), Tuberous Sclerosis Complex (TSC):
  - Seizures
  - Usually adjunct therapy, not primary
- ALL other uses are off-label
- Under investigation for other potential disease states

Potential Side Effects Cannabidiol

- CNS: somnolence
- Hepatic damage
- Psychiatric: worsening depression, suicide ideation and behavior
- Seizure activity: wean down slowly to decrease risk of increased seizures
- Weight loss

Potential Med Interactions Cannabidiol

- Medications metabolized by CYP3A4, CYP1A2
  - Increased and decreased levels, action, side effects
  - Some examples: caffeine, diazepam, everolimus, phenytoin, ketoconazole rifampin, stiripentol (Diacomit), theophylline, tacrolimus, tizanidine, warfarin
- Increased risk of hepatic damage with: valproic acid, divalproex, clobazam
- Increased side effects: benzodiazepines, opioids, other CNS depressants

Potential Disease Interactions Cannabidiol

- Pregnancy, breastfeeding, elderly (over 55): data on use lacking
- Psychiatric: see side effects, much higher risk if baseline psychiatric disease state

Potential Therapeutic Uses Nabilone

- FDA approved antiemetic:
  - Cancer patients who failed all other agents
  - Schedule II
    - High potential for abuse
    - **Prescribe only enough for 1 chemo cycle**
    - **Never recommended 'as needed' or prior to failure of other antiemetics**
- ALL other uses: off label, **not** recommended
  - most commonly: to increase appetite in AIDs patients or treat neuropathic pain

Some Side Effects of Nabilone

- High risk of misuse
- High risk cns + psychotomimetic rxns: depression, hallucinations, psychosis, anxiety, ataxia, euphoria, somnolence, disorientation, depersonalization, asthenia, sleep disturbance
- Cardiac: orthostatic hypotension, palpitations, htn, arrhythmia, CVA, syncope, tachycardia
- Other: anemia, leukopenia, body pain, visual disturbance, dry mouth, headache, nausea, tinnitus, gastritis, possibly withdrawal

Potential Med Interactions Nabilone

- CNS depressants:
  - especially alcohol, sedatives, hypnotics, psychoactive substances
- Potentially same as cannabinoids
- Metabolism not completely understood yet
  - Potentially primarily biliary excretion once metabolized
- Highly protein bound: impact unknown
- CYP450 interactions not fully known

Potential Disease Interactions Nabilone

- Substance use disorders: abuse potential not fully known
- Psychiatric disorders: may worsen
- Unknown, not studied:
  - Hepatic/Renal impairment
  - qt prolongation
  - Pregnancy, nursing, elderly, pediatric

CYP450 Information

- FDA detail information: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
- NIH detailed information: https://www.ncbi.nlm.nih.gov/books/NBK557698/
- Best to check individual meds and how metabolized

Questions?

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References

- O'Donnell B, Meissner H, Gupta V. Dronabinol. [Updated 2023 Sep 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557531/
- Meissner H, Cascella M. Cannabidiol (CBD) [Updated 2024 May 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556048/
- Buck, J. Stewart MD1; Bloomer, Ainsley K. BS1; Wally, Meghan K. MSPH1; Seymour, Rachel B. PhD1,a; Hsu, Joseph R. MD1. The Current Evidence for Marijuana as Medical Treatment. The Journal of Bone and Joint Surgery 102(23):p 2096-2105, December 2, 2020. | DOI: 10.2106/JBJS.20.00269
- Rodriguez CEB, Ouyang L, Kandasamy R. Antinociceptive effects of minor cannabinoids, terpenes and flavonoids in Cannabis. Behav Pharmacol. 2022 Apr 1;33(2&3):130-157. doi: 10.1097/FBP.0000000000000627. PMID: 33709984
- Sideli, Luciaa; Trotta, Giuliaa; Spinazzola, Edoardoa,b; La Cascia, Caterinac; Di Forti, Martad,e,f,*. Adverse effects of heavy cannabis use: even plants can harm the brain. PAIN 162():p S97-S104, July 2021. | DOI: 10.1097/j.pain.0000000000001963
- Perisetti A, Goyal H. Endocannabinoid system and cannabis hyperemesis syndrome: a narrative update. Eur J Gastroenterol Hepatol. 2022 Jan 1;34(1):1-8. doi: 10.1097/MEG.0000000000001992. PMID: 33208685
- Aggarwal SK. Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. Clin J Pain. 2013 Feb;29(2):162-71. doi: 10.1097/AJP.0b013e31824c5e4c. PMID: 22367503
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
- https://doi.org/10.1111/bcpt.13152
- *CMAJ* 2020 March 2;192:E206. doi: 10.1503/cmaj.191097
- https://www.fda.gov/news-events/press-announcements/statement-fda-warning-about-significant-health-risks-contaminated-illegal-synthetic-cannabinoid
- https://www.emcdda.europa.eu/publications/pods/synthetic-cannabinoids
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018677s011lbl.pdf