Medical Cannabis

Cannabis constituents, dosage forms and patient information

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Financial Interest Disclaimer

The speaker has an indirect financial interest (ownership of stock) in G. W. Pharmaceuticals, a British biopharmaceutical company known for its multiple sclerosis treatment product Sativex, nabiximols.
Objectives

1. Explain the receptor-based effects of endogenous and exogenous cannabinoids
2. List the principal phytocannabinoids and assess data regarding their therapeutic uses
3. Describe the entourage effect and its importance in cannabis dosing
4. Review cannabis dosage forms and differentiate among their pharmacokinetics
5. Employ patient teaching strategies for safe and effective cannabis use.

Endocannabinoid System

- A homeostatic system found in all vertebrates
- Discovered within the last three decades
  - A PubMed search for “endocannabinoid”
    - 1993: 10 citations
    - 2014: 6141 citations
    - 2016: 7848 citations
- Referred to as the endocannabinoid system
  - endogenous system whose components interact with or resemble compounds derived from the cannabis plant called cannabinoids.

The Endocannabinoid System

- Three main components:
  - Receptors
  - Endocannabinoids
  - Regulatory Enzymes
- Also interacts with:
  - phytocannabinoids (plant derived cannabinoids)
  - synthetic cannabinoids
  - indirect agonists
  - antagonists

References:


The Endocannabinoid System

- an internal homeostatic regulatory system
- influences multiple physiological processes
  - modulation of pain
  - seizure threshold
  - appetite
  - digestion
  - mood and other processes.
- may also play a role in regulation of the immune system, tumor surveillance, fertility, bone physiology, the hypothalamic-pituitary-adrenal axis and intraocular pressure.

Receptors

- Cannabinoid receptor-1 (CB1)
  - brain, nervous system, connective tissues and gonadal tissues
- Cannabinoid receptor-2 (CB2)
  - mostly found in the periphery


Location of Cannabinoid Receptors

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<tr>
<th>Location</th>
<th>Structure</th>
<th>Function</th>
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<td>Lymphoid organs</td>
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<td>Smooth muscle, myenteric plexus</td>
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<td>Lung smooth muscle</td>
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<td>CB2 receptors</td>
<td>Periphery</td>
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<tr>
<td>CNS</td>
<td>Cerebellar granule cells mRNA</td>
<td>Coordination of motor function</td>
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Crosford, JL. CNS Drugs 2003; 173(3)
Endocannabinoids

- **N-arachidonoylethanolamine** (also called anandamide or AEA)
  - Anandamide (AEA) is a partial agonist of CB₁ receptors; its affinity and efficacy at CB₂ receptors are low. It is a partial agonist at TRPV1 receptors.
- **2-arachidonoylglycerol** (2-AG).
  - 2-AG is a fully efficacious agonist of both CB₁ and CB₂ receptors.


Regulatory enzymes

- The enzymes that modulate the levels of endocannabinoids are considered to be part of the endocannabinoid system.
  - Some synthesize, some catabolize
    - Fatty acid amidohydrolase (FAAH)
      - Breaks down AEA
    - Monoacylglycerol lipase (MAGL)
      - Breaks down 2-AG
    - N-arachidonoylphosphatidylethanolamine (NAPE)
      - Synthesizes AEA
      - Diacylglycerol (DAG)
      - Synthesizes 2-AG

Endocannabinoid System

- Receptors
  - CB₁
  - CB₂
  - TRPV1 and some other "orphan" receptors

- Endocannabinoids
  - AEA
  - 2-AG

- Enzymes: synthesis
  - AEA – NAPE
  - 2-AG – DAG

- Enzymes: degradation
  - AEA – FAAH
  - 2-AG – MAGL

ECS Imbalance

- **ECS hyperactive**: inflammation, insulin resistance, overweight/obesity, obesity-related cardiometabolic disorders

- CB₁ receptor **inverse agonists** might be effective for weight gain but have the potential for serious side effects.


ECS Imbalance

- **ECS hypoactive**: migraine, fibromyalgia and idiopathic bowel syndromes

- Blockers of anandamide hydrolysis (allowing CB₁ to accumulate) reduce anxiety, pain, cancer growth, and colitis in animal tests.


Cannabinoids: Types

- If naturally occurring in the body, called endocannabinoids
- If naturally occurring in plants, called phytocannabinoids
  - Examples of phytocannabinoids
    - delta-9-tetrahydrocannabinol (THC)
    - cannabidiol (CBD)
    - cannabichromene (CBC)
    - cannabigerol (CBG)
    - tetrahydrocannabivarin (THCV)
    - cannabinol (CBN)
  - Examples of synthetic cannabinoids
    - dronabinol (Marinol)
    - nabilone (Cesamet)

The Entourage Effect

- THC can be co-administered with cannabidiol (CBD)
  - some strains of herbal cannabinoid medicines
  - certain cannabis-based extractions
- Cannabidiol (CBD) antagonizes some undesirable effects of THC:
  - intoxication, sedation and tachycardia
  - contributes analgesic, anti-emetic, and anti-carcinogenic properties in its own right.
- Anxiogenic, dysphoric, and possibly short-term memory-interrupting effects of THC are mitigated

Pharmacological actions of non-psychotropic cannabinoids

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Therapeutic Activity

- **THC** (delta-9-tetrahydrocannabinol) psychoactive cannabinoid
  - plant strains have been selectively bred to increase its percentage content for recreational use

- **CBD** (cannabidiol) no psychoactive properties
  - may positively influence the side-effect profile of cannabis by influencing receptor-binding and metabolism of THC

- Other phytocannabinoids widely varying activity
  - cannabinol, cannabigerol, cannabinone, and tetrahydrocannabivarin

- Terpenes (also called terpenoids) compounds which give cannabis its distinct smell
  - content may differ highly among cannabis varieties
  - may have synergic effects with phytocannabinoids

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Cannabinoids -- THC

- **THC** - The primary psychoactive cannabinoid
  - Most cannabis varieties currently available contain high concentrations - up to 25% by weight - of THC (delta-9-tetrahydrocannabinol).
  - Responsible for many therapeutic effects
  - May also cause dizziness, somnolence and disorientation.

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Cannabinoids -- CBD

- **Cannabidiol** (**CBD**)
  - Possibly the single most important cannabinoid
  - the greatest therapeutic potential
  - May positively influence the side-effect profile of cannabis
  - influences receptor-binding and metabolism of THC.
  - Appears safe for human consumption.
  - Small clinical trial
    - oral administration of 600 mg of CBD
    - 16 subjects
    - no acute behavioral and physiological effects

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References:
Cannabinoids -- CBD

- Limited safety data exist for long-term use of CBD in humans.
- There are no known absolute contraindications to cannabidiol (CBD).
- Chronic use and high doses up to 1,450 mg/day of CBD are reportedly well tolerated in humans.


Cannabichromene (CBC)

Cannabichromene (CBC) is a potent anandamide uptake inhibitor and thus may modulate the endocannabinoid system similarly to CBD.


In mice studies, it has been shown that CBC:
- is active in producing hypothermia and hypomotility (but only at high doses)
- has anti-inflammatory properties
- has analgesic activity


In in vitro studies, it has been shown that CBC:
- has antibiotic and antifungal effects
- is a potent GABA uptake inhibitor, suggesting application in spasticity
- displays analgesic and anti-erythemic effects
- has antifungal properties
- has cytotoxic activity against human epithelioid carcinoma and human breast cancer cells


Cannabigerol (CBG)

- Cannabigerol (CBG) is the phytocannabinoid precursor molecule, and demonstrates weak partial agonism at CB1 and CB2.

- In rodent models, CBG:
  - displays antidepressant properties


- In vitro studies, CBG:
  - is a potent GABA-uptake inhibitor, suggesting application in spasticity
  - displays analgesic and anti-erythemic effects
  - has antifungal properties
  - has cytotoxic activity against human epithelioid carcinoma and human breast cancer cells

Cannabigerol (CBG)

- In vitro studies, CBG:
  - displays anti-hypertensive activity
- In vivo studies, CBG:
  - displayed anti-inflammatory activity
- Tetrahydrocannabivarin (THCV)
  - Tetrahydrocannabivarin (THCV) is a CB1 antagonist at low doses, but displays weak agonistic effects at high doses
  - In obese mice models THCV:
    - reduced appetite
    - produced weight loss
    - decreased body fat and leptin concentrations
- In rodent experiments, it has been shown that THCV:
  - has anticonvulsant properties in cerebellar and pyramidal cortical tissues
  - works via CB1 to diminish carrageenan-induced hyperalgesia and inflammation
  - may exert beneficial effects on bone formation and fracture healing

Cannabinol (CBN)

- Cannabinol (CBN) is the oxidative byproduct of THC and appears after long storage. It is a weaker partial agonist at CB1, and CB2, as compared to THC.
  - In vitro studies, it has been found that cannabinol is:
    - anticonvulsant
    - anti-inflammatory
  - In vivo studies, CBN has been shown to:
    - reduce ketamine-induced paw edema
    - reduce cytokine levels
    - reduce pain behavior
    - reduce inflammation
    - stimulate bone formation

References:
Metabolism

- Metabolites contribute significantly to cannabis’ effects
- Δ9 THC metabolized to 11-OH-THC by CYP2C and CYP3A4 when absorbed in the small intestine
  - greater activity of metabolite at CB1 receptors in the brain
  - with inhalation (vs. ingestion) Δ9 THC delivered directly to brain
- CBD metabolized to 7-OH-CBD & 6-OH-CBD
  - little research on their properties
- CBD competitively inhibits THC metabolism resulting in a longer action at a lower intensity
- CBD is a strong CYP450 inhibitor for many drugs when administered in pure form in research settings

Cytochrome-mediated metabolism

- Inhibitors of 2C9, 2C19, and 3A4 may increase the effect and duration of THC
  - macrolides, OCS, CBD, paroxetine, fluoxetine, some PPIs, Ca++ channel blockers, antifungals, HIV antiretrovirals
- Inducers of 2C9, 2C19, and 3A4 may decrease the effect and duration of THC
  - Carbamazepine, rifampin, phenytoin, ritonavir, St. John’s Wort, phenobarbital

Cytochrome-mediated metabolism

- THC is a 1A2 inducer
  - May decrease the effect of theophylline, clozapine, chlorpromazine
- CBD is a 3A4 and 2D6 inhibitor
  - May increase the bioavailability and effect of macrolides, CCBs antihistamines, haloperadol, sildenafil
- Clinicians should monitor patients who are concomitantly consuming high doses of cannabis with other medications that are metabolized by the CYP2C9, CYP2C19, CYP1A2 CYP2D6 and CYP3A4 enzymes.
Terpenes

- Volatile aromatic molecules
- Evaporate easily
- Provide evolutionary advantage to cannabis plants
- Buffer THC psychoactivity (along with CBD)
- Amplify effects of cannabinoids


Some Important Terpenes


Dispensary Label

Effects of cannabis consumption

- Regardless of the specific physiological system, the effects of cannabis are dependent on many factors.
  - Dose of cannabis consumed
  - Route of administration
  - Timing – the effects of cannabis are different right after consumption as compared to hours after consumption
  - Health status of the patient
  - Age of the patient
  - Co-administration of other drugs/medicines
  - Whether or not the patient has been receiving medical cannabis therapy long-term or if the patient is cannabis-naïve

Administration of Cannabis

- (1) Smoking and vaporization of whole dried plant
- (2) Liquid, oil or solid preparations for vaporization
- (3) Liquid or oil preparations for metered oromucosal or sublingual administration or administration per tube
- (4) Oral administration of edibles, teas, beverages, etc.
- (5) Topical forms and the cannabis patch

Inhalation of Cannabis

- Cannabis is often inhaled – either through a cigarette (joint), pipe, water pipe (also known colloquially as a ‘bong’), or vaporizer.
- Many consumers prefer inhalation to ingestion because cannabis’ effects are almost immediately experienced after inhalation.
- This outcome allows one to moderate the dose as needed or in accordance with one’s particular preference, as well as to achieve immediate relief from pain, nausea, and other symptoms.

Oral and Oromucosal Cannabis Dosing

- Orally administered cannabis is particularly difficult to titrate. Effects may not be appreciated for 2 hours after consumption
- Cannabis products may not be uniform from purchase to purchase
- A personal “bioassay” of the effects of a cannabis product should be performed each time that a new supply is acquired
- By starting with a low dose, allowing adequate time between doses for the cannabis to take effect, and titrating the dosage slowly, over several days to weeks, a patient should be able to avoid overdosing

Cannabis Dosing: THC in Mg.

- Average adult dose of THC for:
  - Cannabis-naïve patient: 2.5-5 mg
  - More experienced patient: 10-20 mg
  - Heavy user: 25 mg or more

- To convert % THC/gram to milligrams, move the decimal one place to the right:
  - e.g., 21.23 % THC + 212.3 mg THC per gram of cannabis
  - The same conversion could be done for other cannabinoids and terpenoids (e.g., 0.39 % β-caryophyllene = 3.9 mg per gram of cannabis)

CBD:THC Proportions

- 0:1 Significant “high” (especially if over 30 mg THC ingested)
  - Euphoria, confused thought, uncontrolled laughter.
  - Strong side effects: tachycardia, anxiety, tension
- 1:2 Noticeable “high” effects
  - Euphoria, laughter and thoughts more calm.
  - Milder side effects: reduced risk of tachycardia, anxiety
- 1:1 Relaxation with very light “high” effects
  - Little euphoria, calmness and tranquility.
  - Few side effects for most users.
- 2:1 Few to no “high” effects.
  - No euphoria, sedation, light-headedness, or dizziness.
  - Practically no psychoactive effects.
- 1:0 No “high” effect, at all.
  - Normal mood.
  - No psychoactive effects
Cannabis Dosage: Smoking

- The active ingredients in cannabis—\(\Delta^2\)-tetrahydrocannabinol (THC), cannabidiol (CBD) and other phytocannabinoids, as well as terpenoids—are vaporized by the heat of combustion and inhaled.
- Inhaled constituents quickly pass from alveoli into the bloodstream and readily cross the blood-brain barrier.
- This short onset of action makes dose titration possible, by spacing inhalations at intervals.


Cannabis Dosage: Smoking

- Similar to IV bolus
- Passive diffusion into alveolar capillaries
- Rapid onset (seconds to minutes)
- Peak effect by 15-30 minutes, lasting 2-3 hours
- Elimination \(t_{1/2}\) ~20 hours (2-13 days)
- Elimination via feces (65%) and urine (20%)


Cannabis Dosage: Smoking

- Cannabis flowers typically 8 – 25% THC (1 gm contains 80 – 250 mg of THC)
- Average amount of whole plant cannabis in a rolled joint 0.5-1 gm (40 -125 MG THC)
- With reasonably high potency cannabis flowers, 1-3 hits is generally enough, even for experienced users
- Average frequency of use 1-6 x/day
- Average amount used daily may range from 1-12 grams or more

Effects of Smoking

- Some studies have failed to link cannabis inhalation adverse pulmonary effects associated with tobacco smoking.
- Other studies suggest an association between smoking cannabis and cancer.
- Still other studies suggest that cannabis does not have negative effects on the respiratory system.


Vaporization

- **Vaporization:** smokeless inhalation delivery system
- **Warm air or heat of 180°C to 210°C (356-410°F) rather than a flame** is used to convert cannabinoids and other compounds into a fine mist that can be inhaled.
- Cannabinoids and terpenoids boil between 155-250°C (311-482°F)
- **Ideal temperature is 210°C (410°F)**


- **Vaporizers** heat herbal cannabis to the boiling point of cannabinoids and terpenoids but well below the combustion point of herbal cannabis, so no smoke and relatively little tar is generated.


Abrams et al. study showed:
- carbon monoxide levels lower in patients who consumed marijuana via vaporization as compared to patients who consumed marijuana via smoking.


**Types of Vaporizers**

- **Safety, capabilities and size of the vaporizer**
- Vaporizing pens are the smallest and typically have the least power.
- **Portable vaporizers** pocket-sized.
- **Desktop vaporizers** largest, require electrical outlet.
- **Vapor cannot be stored in the collection balloon**
  - condensation of the vaporized cannabinoids occurs.
  - limit the amount of vapor in the balloon to the amount that one plans on inhaling within a ten-minute period.
Convection-based Vaporizer

- Vaporizer System for the Administration of Marijuana.
- The cannabis is placed in the chamber and heated to a temperature below that required for combustion. The balloon fills with vapor that contains the active ingredients without the tar or particulates thought to be responsible for most of the drug’s adverse effects on the respiratory tract. The patient inhales the vapor from the balloon.


Conduction-based Vaporizer

Hand-held Vaporizers
Vaporization of Whole Plant Cannabis

- Vaporizers may require as much as twice as much plant material to deliver the same dose as smoking (i.e. 2 gm/dose, depending on vaporizer efficiency)
- The Volcano desktop vaporizer was shown in one study to deliver a similar percentage of available THC to smoking (36-61%)
- Absorption may be faster with vaporization, duration of activity is similar to smoking
- Effects last 2-4 hours
- Frequency of use 2-6 x daily

Vaporization of Concentrates

- Concentrates (kief, hash, oil, wax, shatter) are plant extracts
  - may be missing some parts of the entourage
- Much less weight/volume is required
  - 0.1 gm wax might provide 65 mg of cannabinoids
  - some concentrates have higher concentrations of particular terpenes than the whole plant
  - terpenes generally vaporize at a lower temperature than cannabinoids
  - terpenes may have specific therapeutic effects

Traditional Hashish
Dropping a “dab” to vaporize

Oral-mucosal Route

- Effects begin to develop in less than an hour or up to 2.5 hours after administration.
- Duration 2 hours, or 5-6 hours if swallowed.
- Peak effects ~1.5 - 4.25 hours after administration.
- Onset and peak plasma concentrations somewhat sooner than oral.
- Oromucosal administration may be more desirable than oral for nausea.
- May be easier to titrate dose than with oral administration.
Oral-mucosal Route

- Absorption can be rapid but peak effects may be delayed
- Effects can also be long-lasting
- Some fraction of the dose is usually swallowed rather than sublingually absorbed.
- Effects may be evident within 15-30 min but may not peak immediately.
- Mouth strips, lollipops, and lozenges may also provide for sublingual administration.
Oral-mucosal Route

- Tinctures: extracts of cannabis in alcohol or glycerin
- the primary way in which cannabis medicines were delivered prior to their removal from the USP
- can be taken sublingually in drops or spray
- sublingual absorption has the potential to avoid first-pass metabolism.
- Tinctures may also be mixed with a beverage and swallowed with similar effect to other oral forms.

Oral Consumption

- Available forms: butter, oil, capsules, baked goods, candies, tea, honey
- For cannabis effects to develop, the orally consumed material must be digested.
- Effects may take up to two hours to develop, peak at 2-3 hours, and may last for 4-12 hours.
- Naïve users can easily overdose on edibles
- May require much larger amounts of cannabis (3-5 times) to achieve desired effect.


Prescription Cannabinoids

- Two oral cannabinoid medications available in North America: nabilone (Cesamet) and dronabinol (Marinol)
- Active within 30-90 minutes of dosing, with effects lasting up to 6-8 hours.
- Absorption from the GI tract is variable with generally low bioavailability
- Side effects: principally drowsiness, dizziness and dry mouth.

A Comment on Nabilone and Dronabinol

- Synthetic THC
- Re-scheduled to Schedule III in 1999
- May be problematic even for experienced cannabis users
- Tends to produce dysphoria rather than euphoria
- Dose is often too high
- Effects are erratic
- Very expensive

Topical

- Cannabis products can be applied topically for arthritis, muscle spasm, pain or inflammation
- Also used for psoriasis, dermatitis, dry skin
- Probable to oldest use of cannabis as medicine
- Extracted into alcohol, oil or salve for topical administration.
- Minimal absorption into the bloodstream so minimal psychoactive effects
- Little research exists
Topical

- Dose is determined by area to be covered
- Duration of action has not been studied, but, once absorbed, effects are reported by patients last up to 4 hours or more
- Typically applied 4 times daily
- More plant material may be required to prepare topicals than for other dosage forms
Transdermal

- Transdermal cannabis patch now also available
- Formulated like nicotine patches
- Gradually release 10—20mg of cannabinoids through dermal absorption
- No first-pass effect—effects felt within 15 min
- Sustained effect for 8-12 hours
- Can be cut to adjust dose
High dose oral cannabis

- Capsules containing 25 – 100 mg cannabinoids in oil per capsule (Cannador)
- Oil concentrates containing up to 800 mg/ml of cannabinoids (provided in a syringe)
- “Rick Simpson oil” protocol recommends up to 1 gram of 90% cannabinoid oil per day, containing 900 mg of cannabinoids
- “CBD oil” produced from legally grown industrial hemp

Safety of Cannabis

- With regard to cannabinoid botanicals, the Institute of Medicine concluded after a comprehensive government-commissioned review published in 1999 that “except for the harms associated with smoking, the adverse effects of marijuana [cannabinoid botanicals] use are within the range of effects tolerated for other medications.”
Overconsumption

- There have been numerous reports of overconsumption of cannabis-infused products by those not waiting an adequate amount of time for the cannabis to have an effect.
- Re-dosing (particularly of orally administered cannabis) should be based on the fact that individuals who ingest cannabis may not begin to experience psychoactive or physiological effects of oral consumption for 120 minutes after ingestion.
- Overconsumption of cannabis-infused edible products (or oral cannabis medicines) may be associated with hostile behavior, erratic speech and adverse psychological effects.


The LESS Method

The L.E.S.S. Method: A Measured Approach to Oral Cannabis (or How Not to Overdose on Oral Cannabis)

Start Low
Establish Potency
Go Slow
Supplement as Needed.

https://www.erowid.org/plants/cannabis/cannabis_article1.shtml

The LESS Method

- If one is faced with an edible of unknown potency, and yet is determined to try it, the best way to avoid an overdose is to intentionally underdose.
- Begin with a small piece (less than a quarter of a suggested portion). Measure, photograph or weigh the piece you try and make note of it.
- Then wait a minimum of 90 minutes on an empty stomach, or 120-150 minutes otherwise, before evaluating whether or not to consume another small piece.