Medical Cannabis

Cannabis constituents, dosage forms and patient information

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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 some 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
    - 2018: 27,538 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
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.

1) 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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<thead>
<tr>
<th>Location</th>
<th>Structure</th>
<th>Function</th>
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<td>CNS</td>
<td>Hippocampus</td>
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<td>Periphery</td>
<td>Lymphoid organs</td>
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<td>Duodenum, ileum, myenteric plexus</td>
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<td>Lung smooth muscle cells</td>
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<td></td>
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<tr>
<td>Periphery</td>
<td>Lymphoid tissue</td>
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<td>Peripheral nerve terminals</td>
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<td></td>
<td>Retina</td>
<td>Intraocular pressure</td>
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<tr>
<td>CNS</td>
<td>Cerebellar granule cells mRNA</td>
<td>Coordination of motor function</td>
</tr>
</tbody>
</table>

Croxford, J.L. (2003) CNS Drugs 17(3)

2) 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.

3) 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
  - Monoacetylglcerol lipase (MAGL)
    - Breaks down 2-AG
  - N-arachidonoylphosphatidylethanolamine (NAPE)
    - Synthesizes AEA
  - Diacylglycerol (DAG)
    - Synthesizes 2-AG


The Endocannabinoid System in the Nervous system

"Complex, Redundant Promiscuous"

Endocannabinoid System

- **Receptors**
  - CB₁
  - CB₂
  - TRPV1 and some other “orphan” receptors

- **Endocannabinoids**
  - AEA
  - 2-AG

- **Enzymes:**
  - synthesis
    - AEA → NAPE
    - 2-AG → DAG
  - degradation
    - AEA → FAAH
    - 2-AG → MAGL

**ECS Imbalance**

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

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


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**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 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


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
  - cannabiol, cannabigerol, cannabichromene, and tetrahydrocannabinvarin.

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

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.


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.

Karniol IG, Carlini EA (1973) Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol. Psychopharmacologie 33(1):53-70

- Appears safe for human consumption.
- Small clinical trial
  - oral administration of 600 mg of CBD
  - 16 subjects
  - no acute behavioral and physiological effects

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 in vitro studies, it has been shown that CBC:
- has antibacterial and antifungal effects superior to THC or CBD
- has cytotoxic activity in certain cancer cell lines


Cannabichromene (CBC)

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: decreases prostaglandin synthesis
- has analgesic activity
  

- has antidepressant activity
  
  

Cannabigerol (CBG)

- Cannabigerol (CBG) is the phytocannabinoid precursor molecule of THC, CBD, & CBC and is a weak partial agonist at CB₁ and CB₂ receptors

- In rodent models, CBG:
  
  - displays antidepressant properties (inhibits serotonin and norepinephrine uptake)
  

- In 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 in vitro studies, CBG:
  - displays **anti-hypertensive activity**
  - inhibits keratinocyte proliferation and this suggests that CBG has application in **psoriasis therapy**
  - has **antibacterial effects** against Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - is a **α-2 adrenoreceptor agonist**, and **5-HT\textsubscript{1A} antagonist**
  - blocks lipoxygenase (anti-atshmatic)

Tetrahydrocannabivarin (THCV)

- Tetrahydrocannabivarin (THCV) is a CB\textsubscript{1} antagonist at low doses, but displays weak agonist effects at high doses. Has 20-25\text% of THC’s psychoactivity, with quicker onset and briefer duration.
- Not a metabolite of Marinol (**biomarker of illicit use**)
  ElSohly et al. (1999) Delta-9 THCV as a marker for ingestion of cannabis. *J Anlyt Toxicol* 23(3) 222-4
- 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 pyriform cortical tissues
    - works via CB\textsubscript{2} to **diminish carageenan-induced hyperalgesia** and inflammation, as well as formalin-induced pain behaviour
    - may exert **beneficial effects on bone formation and fracture healing**
Cannabinol (CBN)

- Cannabinol (CBN) is the oxidative by-product of THC and appears after long storage. It is a weaker partial agonist at CB1 and CB2 as compared to THC. Potentiates THC effects.

- In in vitro studies, it has been found that cannabinol is:
  - anticonvulsant
  - anti-inflammatory
  - potent against MRSA (MIC 1 μg·ml⁻¹)
  - reduces keratinocyte proliferation
  - stimulates mesenchymal stem cells in marrow suggesting stimulation of bone formation

Metabolism

- Metabolites contribute significantly to cannabis’ effects
  - Δ⁹ THC metabolized to 11-OH-THC by CYP2C9 and CYP3A4 when absorbed in the small intestine
    - with inhalation (vs. ingestion) Δ⁹ THC delivered directly to brain
    - greater activity of metabolite at CB1 receptors in the 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
  - When administered in pure form in research settings, high doses of CBD can be a strong CYP450 inhibitor for enzymes that metabolize many drugs

Cytochrome-mediated metabolism

- **Inhibitors** of 2C9, 2C19, and 3A4 may **increase** the effect and duration of THC
  - Erythromycin & clarithromycin [not azithromycin], OCs, CBD, paroxetine, fluoxetine, some PPIs, Ca++ channel blockers, antifungals, HIV antiretrovirals, itraconazole, grapefruit juice

- **Inducers** of 2C9, 2C19, and 3A4 may **decrease** the effect and duration of THC
  - Carbamazepine, rifampin, phenytoin, ritonavir, St. John’s Wort, phenobarbital, carbamazepine, dexamethasone [but not prednisone]

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Cytochrome-mediated metabolism

- THC is theoretically a 1A2 **inducer**
  - May **decrease** the effect of theophylline, clozapine, chlorpromazine
  - BUT no relevant induction seen at max doses in human trials

- CBD is a 3A4 and 2D6 **inhibitor**
  - May **increase** the bioavailability and effect of macrolides, CCBs, antihistamines, haloperidol, sildenafil, SSRIs, benzodiazepines
  - Inhibition only seen at doses **significantly higher** than usual max.

- 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

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.”
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.


Principles of Cannabis Dosing

- Limiting the dose of THC is the key to avoiding unwanted effects of cannabis overconsumption

- CBD doses can be gradually increased to achieve desired effects, and there are no specific ceiling doses for CBD

- “Entourage effect” suggests that a small amount of THC (even for those patients who desire none of the THC-specific effects) facilitates CBD activity
Oral and Oro-mucosal 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)
Principles of Cannabis Dosing

- 2.5 mg of THC is a threshold dose, below which even most cannabis-naïve persons will not note any undesirable psychoactive effects.
- Even this low dose may produce psychoactive effects in some individuals.
- Self-titration to determine the THC threshold dose is the first step in determining what the correct dosages are for any individual.
- Patients are encouraged to self-titrate from a below-threshold dose upward to find their THC tolerance.

Principles of Cannabis Dosing

- Once the tolerable dose of THC is determined, patients may gradually increase the amount of CBD used in each dosing interval (up to 2 - 5 mg/lb in some studies).
- This can be done by changing the ratio of THC to CBD or by adding CBD to an established dose of THC in a known product.
- For a cannabis-naïve person, the first step is to establish a tolerable dose of THC.
Principles of Cannabis Dosing

0.5 mg /lb is a basic rule of thumb for starting to calculate CBD dosage

This gives a total dose that should be divided tid or bid

Generally round dosages down:
- Based on available preparations and proportions
- Provide a slightly lesser dosage to start
- Some preparations may contain more THC than expected
- Advise patient that dosage can be gradually increased within above basic parameters

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.


Principles of Cannabis Dosing

Changing the ratio may increase the THC dose while holding the CBD dose steady:

- One product line provides:
  - 16 mg of CBD per ml
  - 8:1 = 16mg CBD/2 mg THC
  - 4:1 = 16mg CBD/4 mg THC
  - 2:1 = 16mg CBD/8 mg THC
  - 1:1 = 16mg CBD/16 mg THC

Or the THC dose may be constant, regardless of the CBD dose

- Another product line provides:
  - 20:1 = 20mg CBD/1 mg THC
  - 1:1 = 1mg CBD/1 mg THC
  - 2:1 = 2 mg CBD/1 mg THC

Or there the amounts of total cannabinoids may be constant, with only the ratios changing

- A third product line provides:
  - 20:1 = 9.5mg CBD/0.5 mg THC
  - 8:1 = 8.9 mg CBD/ 1.1 mg THC
  - 4:1 = 8 mg CBD/2 mg THC
  - 10 mg of total cannabinoid per ml

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.