Cannabis and Dentistry

James J. O'Donnell III MS PhD

Assistant Professor

College of Pharmacy, Chicago Medical School

Rosalind Franklin U. of Medicine and Science

Objectives:

- Recall the distribution of Cannabinoid receptors CB-1 and CB-2 at the organ system level as well as the cellular level.
- Describe the MOA of THC, and detail the THC signaling which explain physiological effects that underly proven and potential medical uses as well as known side effects.
- Differentiate the physiological effects of CB-1 and CB-2 agonism, and describe their respective mechanisms.
- Recall the FDA-approved and off-label medical uses of THC, assess the strength of evidence behind their efficacy, and recall MOAs and indications of FDA-approved cannabis drugs.
- Describe the possible MOA's, side effects, and indications of cannabidiol (CBD) and assess its utility for medical use.
- Describe the mechanistic differences between THC and illicit synthetic marijuana (e.g., K2) based on receptor selectivity and potency.
- Recall the respective MOAs and indications of medical cannabinoids such as dronabinol, nabilone, and nabiximols.
- Describe the potential therapeutic applications of cannabis to dentistry, and assess the weight of evidence supporting them.
- Describe acute and chronic side effects and drug-drug interactions of cannabis that are relevant to the practice of dentistry.
- Describe appropriate strategies by which dentists may change their practice when treating acute or chronic THC users.

Outline

- Claimed medical applications of cannabis in dentistry
- Cannabinoid Distribution
- Physiological Effects of CB-1, CB-2 Agonism at cellular and organ level
- Current FDA-approved and off-label indications for THC and CBD
- Evaluation of cannabis as potential therapeutic in dentistry
- Cannabis side effects relevant to the practice of dentistry
- Drug-drug interactions of cannabis with drugs used in dentistry

Proposed Uses of Cannabis in Dentistry

- Claimed Properties: analgesic, antimicrobial, anti-inflammatory, anxiolytic, anticancer

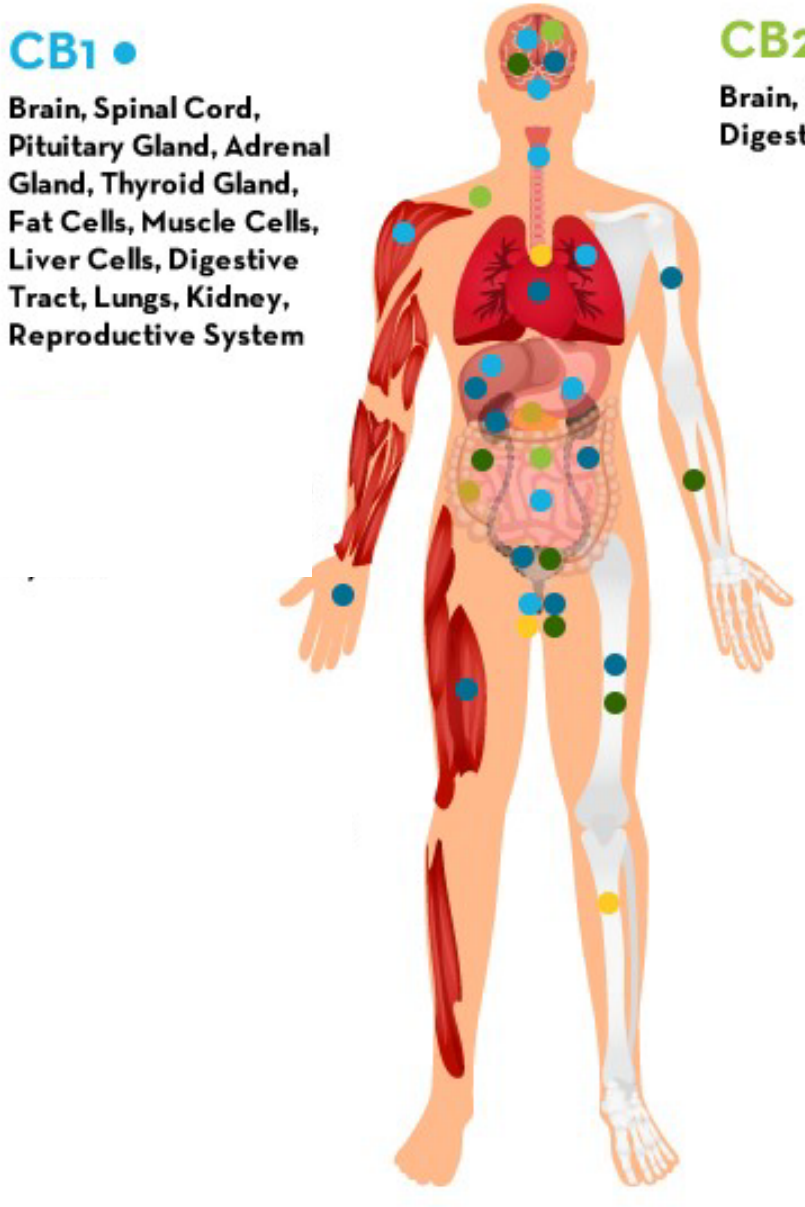
- Proposed indications include:
  - Prevention and treatment of Dental caries, Gingivitis, Periodontal disease
  - Analgesia and anti-inflammatory activity for microbe-induced diseases above
  - Analgesia for cracked teeth, sensitive teeth, pain of surgery, neuropathic pain conditions
  - Dental anxiety treatment
  - Oral cancers

Active compounds of marijuana

- THC is the main active compound in marijuana
  - THC stimulates Cannabinoid receptor 1 and 2 (CB-1 and CB-2)
- Cannabidiol (CBD) not as active; putative targets are more complex

Where are the CB-1 and CB-2 receptors located?

Distribution of Cannabinoid receptors



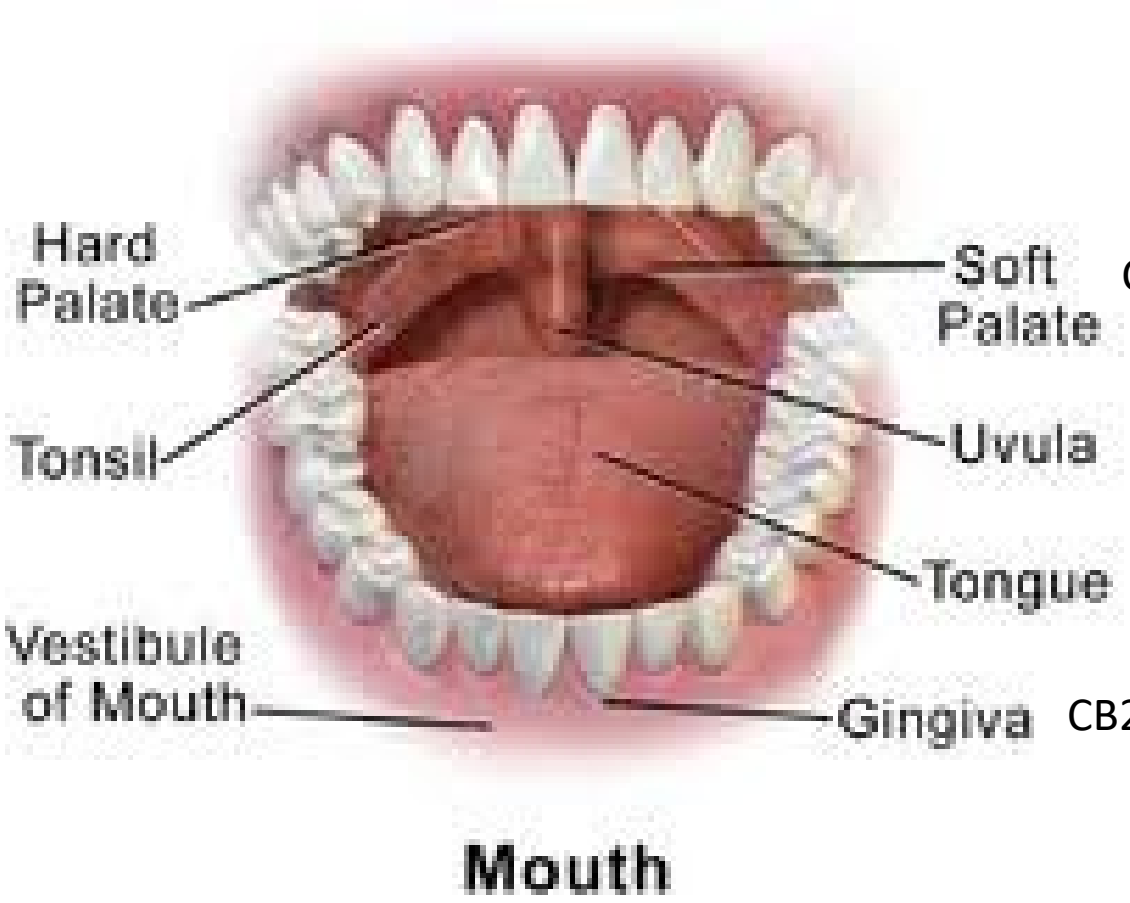
- CB1
  - CNS and peripheral nervous system
  - Many other organs, immune cells

- CB2
  - immune cells + peripheral organs w/ immune function
    - Immune cells: Macrophages, leukocytes
    - Peripheral organs: spleen, tonsils, thymus
  - Only found in brain in disease states
    - immune cell activation and inflammation => CB2 upregulation (in glial cells)

CB-1 Distribution in the Brain

- Brain Regions Expressing CB-1 and their function
  - Basal ganglia nuclei: Initiation of movement; Action selection
  - Cerebellum: balance, coordination
  - Hippocampus: learning + memory
  - Cortex: higher-order functions (sensation, perception, memory)
  - Hypothalamus (less expression): appetite
- Presence of CB-1 in these brain regions suggest that CB-1 agonists may be modulating the functions associated with these regions
- Expression in CNS > Expression in peripheral nervous system
- Expressed on terminals of neurons

Cannabinoid Receptor Distribution in the Mouth



CB2 > CB1 (strongest in base layer)

CB1, CB2 (cytoplasm of epithelium)

CB2, CB1 (epithelium, connective tissue)

- CB receptors also found in: lip, oral mucosa, sebaceous glands, salivary glands, hair follicles

MOA of THC

- Partial agonist at CB-1 and CB-2
- CB-1 and CB-2 are G-protein Coupled Receptors (GPCRs)
- GPCR agonism may increase or decrease cellular signaling, depending on subtype

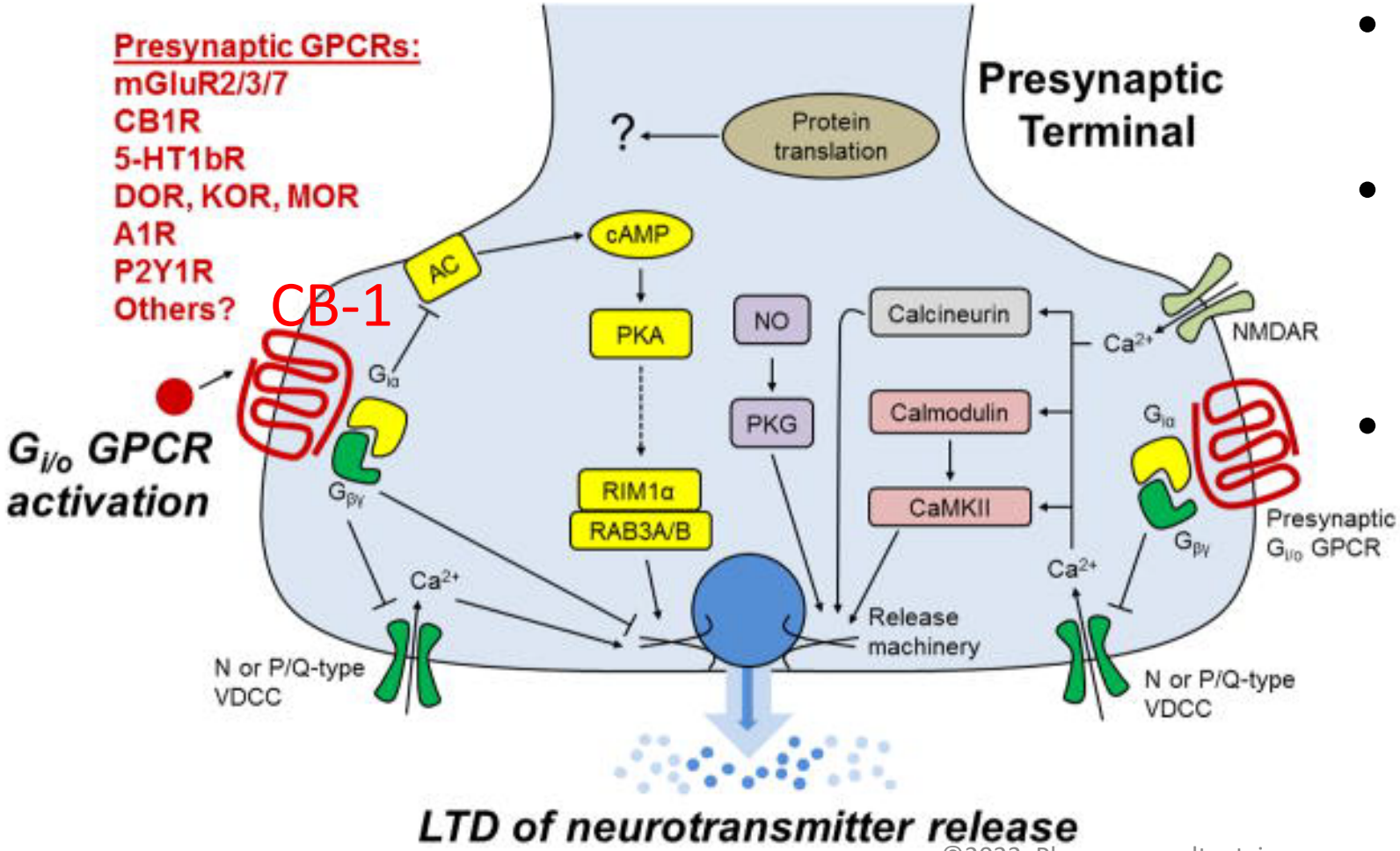
Physiological Effects of THC (CNS-mediated)

- Most prominent effects: euphoria, relaxation
  - Well-being, grandiosity, and altered perception of passage of time also reported
- Dose-dependent effects that sometimes occur:
  - Perceptual changes (e.g., visual distortions)
  - Drowsiness
  - Diminished coordination
  - Memory impairment
  - Dysphoric state
- Rarely (in high doses): visual hallucinations, depersonalization, psychosis

Physiological Effects of THC in Other Systems

- Increased appetite
- Nausea reduction
- Decreased intraocular pressure
- Relief of chronic pain (also CNS)
- Other effects have been observed in different organ systems

Effects of THC at neuronal level: CB-1 agonism decreases neurotransmitter release



- Gα signaling decreases cAMP, decreases NT release via PKA
- $G_{\beta\gamma}$ signaling inhibits Ca2+ influx, which also reduces NT release
- Ion channel modulated may depend on brain region

NT = neurotransmitter

Effects of CB-1 agonism on neurotransmitter systems

- CB-1 agonism provides presynaptic negative regulation, reducing NT release
- Thus, THC generally has a depressant effect on neurons
- CB-1 on presynaptic terminals of GABAergic and glutamatergic neurons
  - GABAergic > glutamatergic
- Due to expression differences, major effect is to inhibit GABA-releasing interneurons
- GABA is inhibitory NT -- “Brakes of CNS”
- Reducing GABA release disinhibits dopaminergic neurons in brain (VTA-mesolimbic pathway)
- Increasing DA levels thought to underly many behavioral effects of THC, including euphoria and addiction

Euphoria and addiction

- GABAergic interneuron inhibition => GABA release reduced
- Less GABA => Disinhibition of DA neurons in VTA-mesolimbic pathway
- DA increase also hypothesized to be related to psychosis side effect

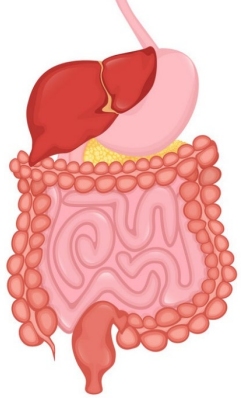
Memory Impairment and Cognition

- CB-1 is expressed in high density in the hippocampus (learning and memory)
- Hippocampus is involved in learning and memory
- CB-1 agonism suppresses NT release at inhibitory and excitatory neurons in short- and long-term manner

Lack of Motor Coordination

- CB-1 expressed in basal ganglia and cerebellum (motor function)
- Acute THC => disrupts autophagy in basal ganglia (striatum)
- Chronic THC use => neuroinflammation in cerebellum

Increase in Appetite: “munchies”

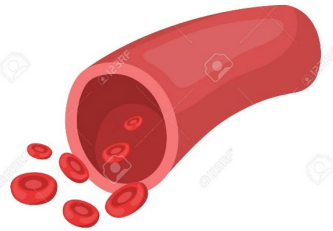


- THC “tricks appetite circuits in brain in hunger mode”
- THC triggers surge in ghrelin, a hormone released by stomach which transmits hunger signal to brain
- Also, THC changed genetic activity of brain cells that respond to ghrelin in hypothalamus (brain region mediating appetite)

Decrease in nausea

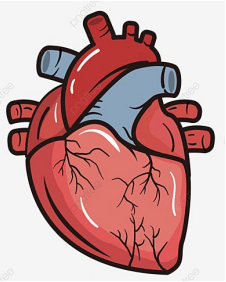
- MOA of nausea decrease is not understood
- Potential MOA: CB-1 agonist reduces GI 5-HT release by enterochromaffin cells
- Cannabinoids block both acute and delayed emesis

Hypotension



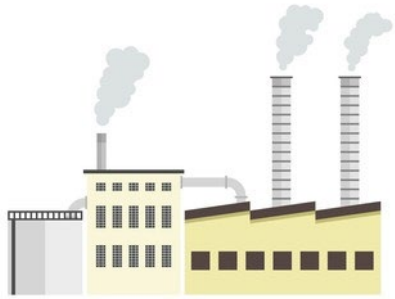
- THC relaxes smooth muscles
- Relaxation of vascular smooth muscle (VSM) => vasodilation
  - Gi signaling => L-type Ca2+ current ↓ => VSM relaxation
- Smooth muscle in stomach, uterus (myometrium), and vas deferens also relaxed

Tachycardia through reflex tachycardia



- THC (in high doses) causes hypotension
- Hypotension can trigger reflex tachycardia

Metabolic effects



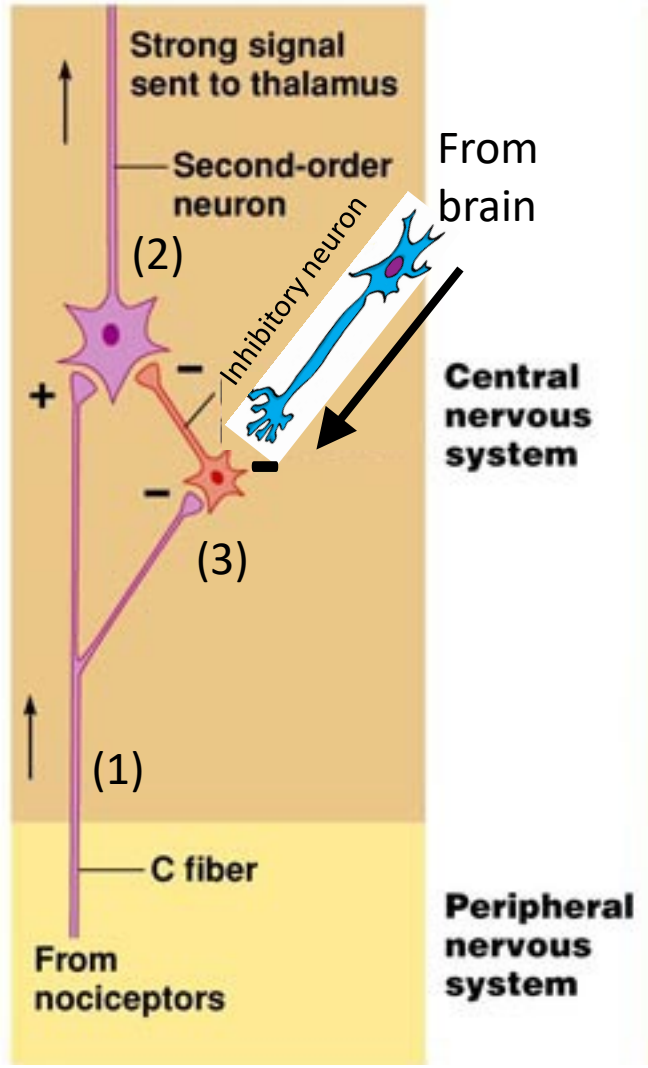
- THC induces lipogenesis in liver => increased bodyweight + adiposity
- Insulin-resistance (insulin-resistant glycogenolysis)
- Gluconeogenesis

- CB receptors are widespread in the body, and there is evidence that it may regulate many organ systems.
- The clinical significance of these physiological effects may depend on the dose of cannabinoid or its potency.
- There is more evidence supporting the clinical significance of some physiological effects compared to others.

Attenuation of pain

Mechanisms of analgesia:

- Inhibition of release of neurotransmitters and neuropeptides from presynaptic nerve endings
  => inhibition of *ascending* pain transmission
- Modulation of postsynaptic neuron excitability
- Activation of *descending* inhibitory pain pathways
- Reduction of neural inflammation



- Moderately effective for chronic pain, especially neuropathic pain
- Pain from M.S. spasticity is one form of neuropathic pain treatable by cannabinoids

Indications of Cannabinoids

- There is “conclusive or significant evidence for benefit from cannabis or cannabinoids” for the following indications (NASEM 2017):
  1) chronic pain
  2) chemotherapy-induced nausea and vomiting
  3) patient-reported symptoms of spasticity associated with multiple sclerosis

Insufficient or no evidence of benefit

Cannabinoids have been proposed as being beneficial for the following conditions:

- Cancer
- Anorexia and wt. loss associated with HIV
- Irritable bowel syndrome
- Epilepsy
- Tourette Syndrome
- ALS
- Huntington's disease
- Parkinson's disease
- Dystonia
- Dementia
- Glaucoma
- Traumatic brain injury
- Addiction
- Anxiety
- Depression
- Sleep disorders
- PTSD
- Schizophrenia and other psychoses

…but "there is insufficient or no evidence upon which to base conclusions about Therapeutic effects" for these indications (NASEM)

THC for epilepsy and PTSD: popular but unproven

- Despite inconclusive evidence for efficacy for these conditions, cannabinoids are used to treat a substantial number of people with PTSD or epilepsy.

Cannabidiol (CBD)

- Brand name: Epidolex
- FDA-approved
- Key MOAs:
  - **enhance activity of 5-HT1a receptors**
  - **negative allosteric modulation of CB1 receptors**
- Other MOAs: Block nucleoside transporters, modulate orphan GPCR GPR55
- Does not bind orthosteric site of CBD-1 or CBD-2
- Potentiates depressant effects of THC while inhibiting its excitatory and emotional effects

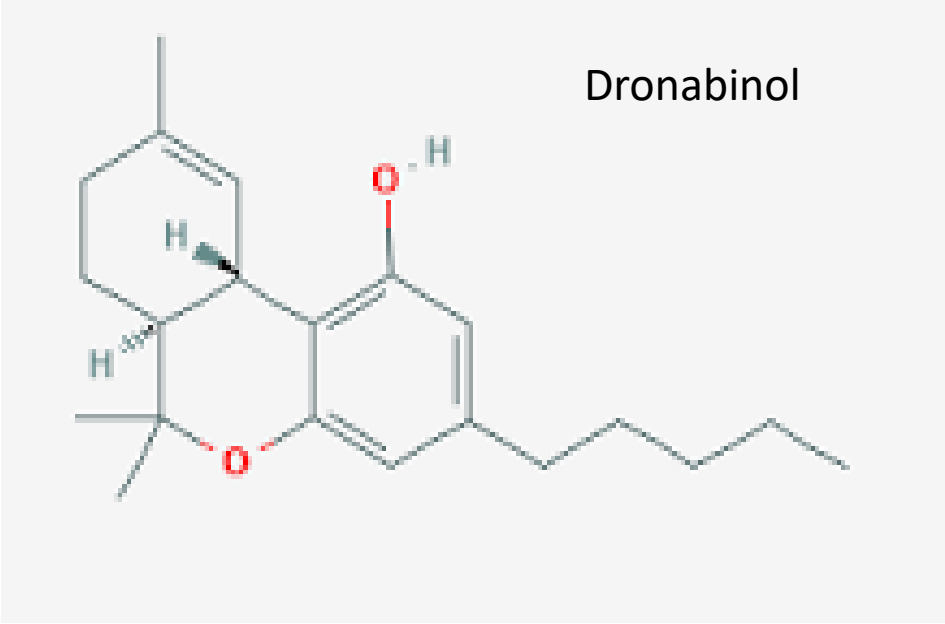
Cannabidiol (CBD)

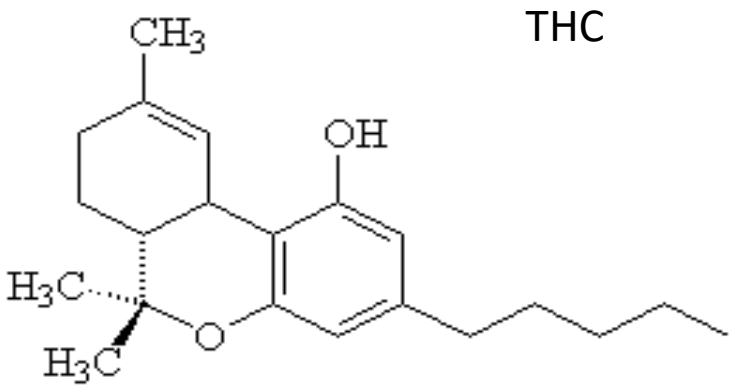
- Brand name: Epidolex
- FDA-approved
- Key MOAs:
  - **enhance activity of 5-HT1a receptors**
  - **negative allosteric modulation of CB1 receptors**
- Other MOAs: Block nucleoside transporters, modulate orphan GPCR GPR55
- Does not bind orthosteric site of CBD-1 or CBD-2
- Potentiates depressant effects of THC while inhibiting its excitatory and emotional effects

Specific Drugs

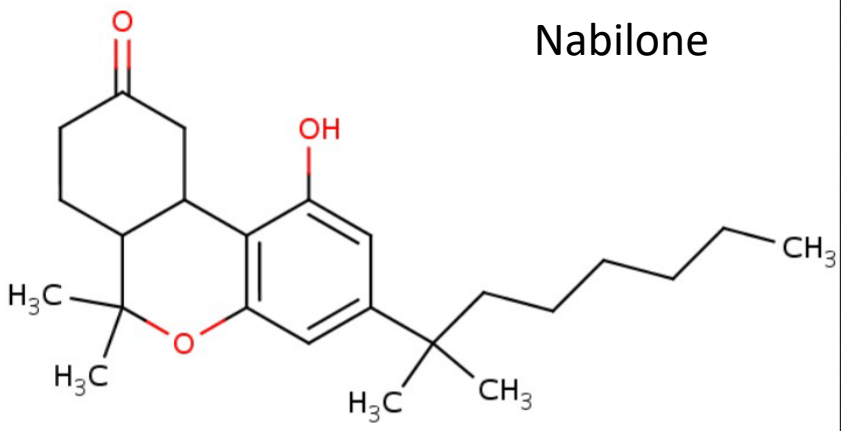
Dronabinol

- Synthetic THC analog
- FDA-approved
- more active enantiomer of THC
- Indications (FDA-approved):
  - Loss of appetite with AIDS
  - Chemotherapy-induced, refractory N/V
- Other indications: post-operative N/V



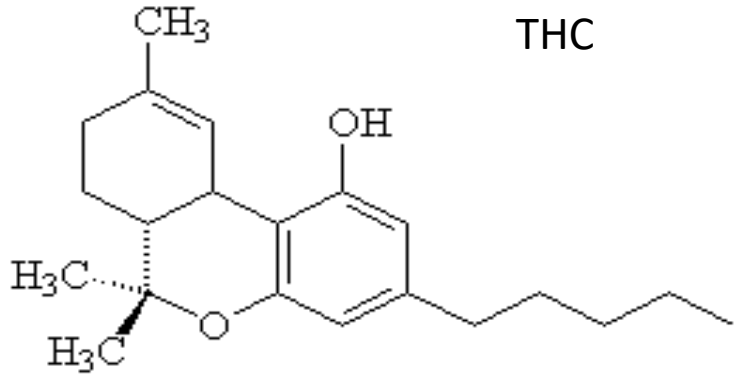


Nabilone



Nabilone

- Older commercial THC analog (reintroduced)
- Indication (FDA-approved):
  - chemotherapy-induced, refractory emesis
- Non-FDA approved indications:
  - N/V in patient w/ AIDS
  - Anxiety
  - Dystonia
  - Glaucoma
  - Post-operative N/V



THC

N/V = nausea and vomiting

Nabiximol

- Botanical drug obtained by standard extraction
- Active components: THC, CBD
- Indication: spasticity associated with Multiple Sclerosis, other neuropathic pain
- In Phase III testing for cancer pain

- Utility of THC-CBD combination: CBD is thought to attenuate some side effects associated with THC

Rimonabant – inverse agonist for CB1 receptor

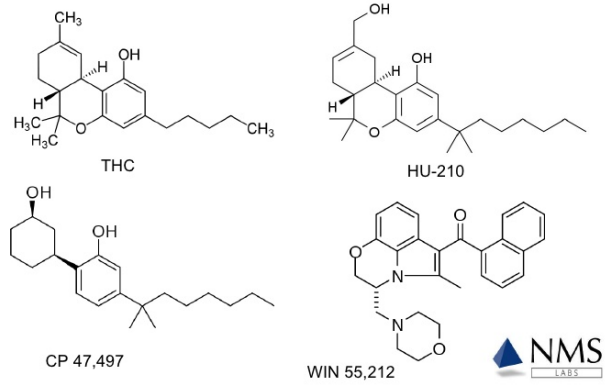
- Initially approved in Europe but withdrawn
- Indication: anorectic for obesity
- Side Effects: suicidality and depression

Frankenstein's Monster: the New Marijuana (K2)

- Potency of illicit cannabis plant material increased 3x in past 20 years
- Physiological effects of active component or marijuana, THC
  - Prominent effects: Euphoria, relaxation
  - Dose-dependent perceptual changes (visual), distortion, diminished coordination, memory impairment
  - Very high doses: visual hallucinations, depersonalization, psychosis, tachycardia

Increased potency

Marijuana to Spice



- Synthetic marijuana chemical structures constantly evolving

  => not chemically related to THC or each other
- Higher efficacy
  - Full agonist to CB1 receptor (THC a partial agonist)
- Synthetic Marijuana Up to 100 times more <u>potent</u> than THC

Applications to Dentistry

Cannabis as Potential Therapeutic in Dentistry

Cannabis as Analgesic

- Chronic pain an accepted indication for THC (esp. neuropathic)
- Pain is a stimulus which triggers compensation in pain transmission pathways
  - Downregulation of mu opioid receptors => opioids less effective for chronic pain, esp. neuropathic
  - Cancer pain is only accepted chronic pain indication for THC
  - Chronic opioid use => increased likelihood of addiction, overdose
- We do not have effective drugs for moderate-severe chronic pain

  $\Rightarrow$Lack of alternatives makes THC use more favorable

- Acute pain (i.e., orthopedic) is not as supported due to existence of more effective drugs although it has efficacy
  - Alternatives: NSAIDS (anti-inflammatory), acetaminophen (pain only), tramadol, opioids (moderate-severe)

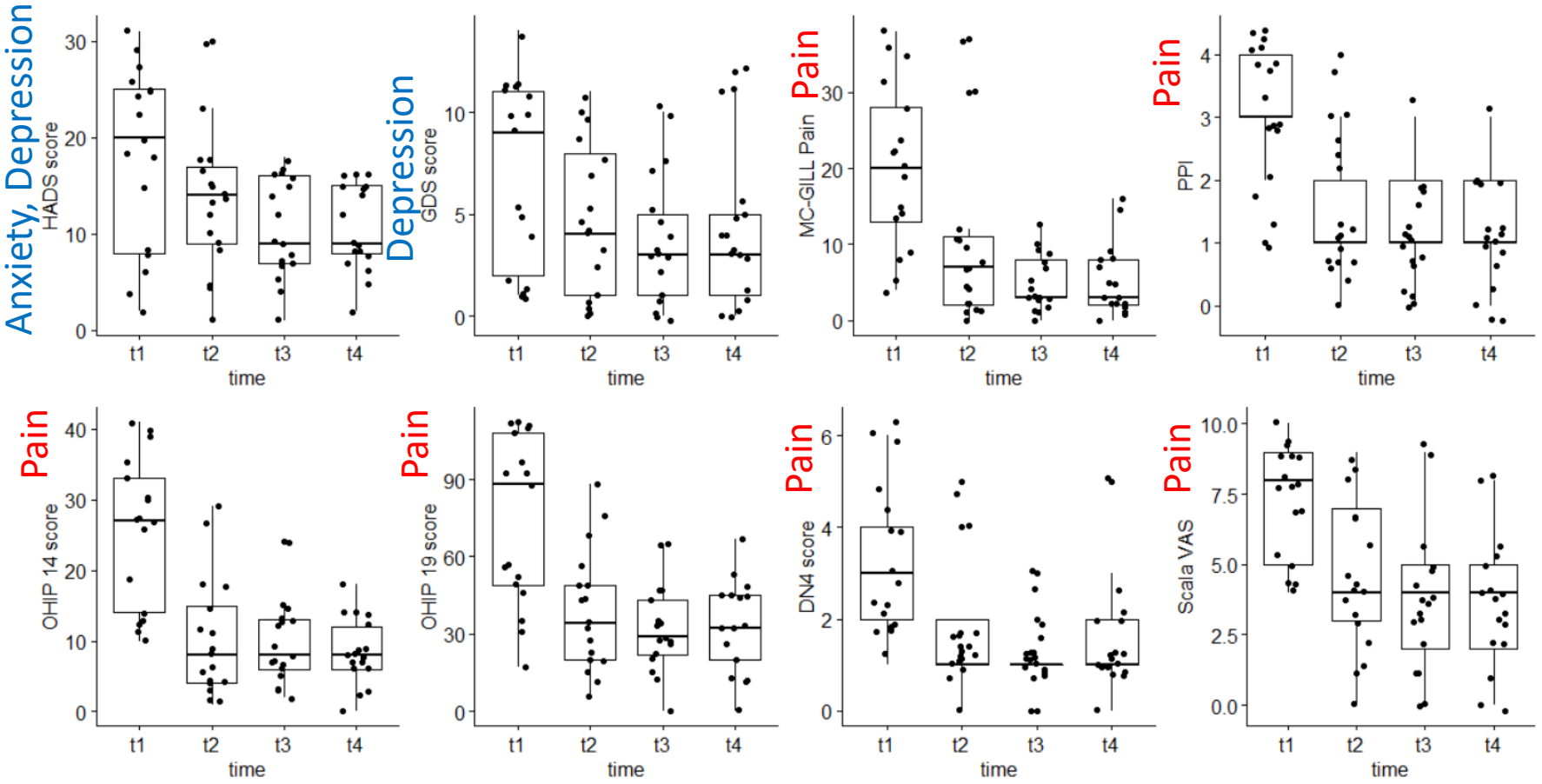
Potential analgesic applications – Acute Pain

- Toothache
  - Underlying pathophysiology
    - irritation, infection, or injury to tooth
    - Hypersensitivity of the nerves
    - Damage to surrounding structures of the tooth
    - Decay of the tooth
- Tooth extractions
- Post-operative pain management

Potential analgesic applications – Neuropathic Pain

- There are a number of oral neuropathic pain conditions
- Burning mouth syndrome investigated w.r.t. cannabis treatment
- Pathophysiology of Burning Mouth Syndrome (hypothesized):
  - Dysregulation of taste and sensory nerves in peripheral NS or CNS
  - In tongue: CB2 ↑, CB1 ↓
  - Pain similar in intensity to toothache

Study: Cannabis Plant Extract for Burning Mouth Syndrome



- Single-arm
- Cannabis plant extract
- 4-wk treatment

*t1=baseline; t2=4 after the end of therapy; t3=12 weeks after t2; t4=24 weeks after t2.

§SCORES. Visual Analogue Scale (VAS), McGill Pain Questionnaire, Present Pain Intensity (PPI), Oral Health Impact Profile questionnaires (OHIP-14, and OHIP-49), Douleur Neuropathique en 4 Questions (DN4), Hospital Anxiety and Depression Scale (HADS), Geriatric Depression Scale (GDS).

Burning Mouth Syndrome: Conclusions

- Change was clinically significant, but not statistically significant (low N)
- Several studies support efficacy and safety of cannabis for burning mouth syndrome

Treatment of Dental Caries and Periodontal Disease

- Rationale: antimicrobial (primary mech) and anti-inflammatory activity of THC and other cannabinoids (CBD, CBG)
  - Particularly antibacterial activity
- Pathophysiology: plaque- and biofilm-forming bacteria, including Streptococcus mutans or Lactobacillus spp.
  - Caused by frequent intake of sugary foods that cause acid build-up, lack of adequate teeth cleaning, and subsequent erosion of enamel

Motivation for studying cannabis as anti-plaque agent

- Chlorhexidine – gold-standard for controlling plaque
- Only chlorhexidine effective at inhibiting dental plaque bacteria growth
  - OTC mouthwashes ineffective for controlling dental plaque
- But…chlorehexidine may cause discoloration as well calcification

- Preliminary study
  - Agar plate streaked with toothpaste or cannabinoid solution
  - Human dental plaque samples were diluted and then spread onto agar plate
  - Bacterial colonies counted

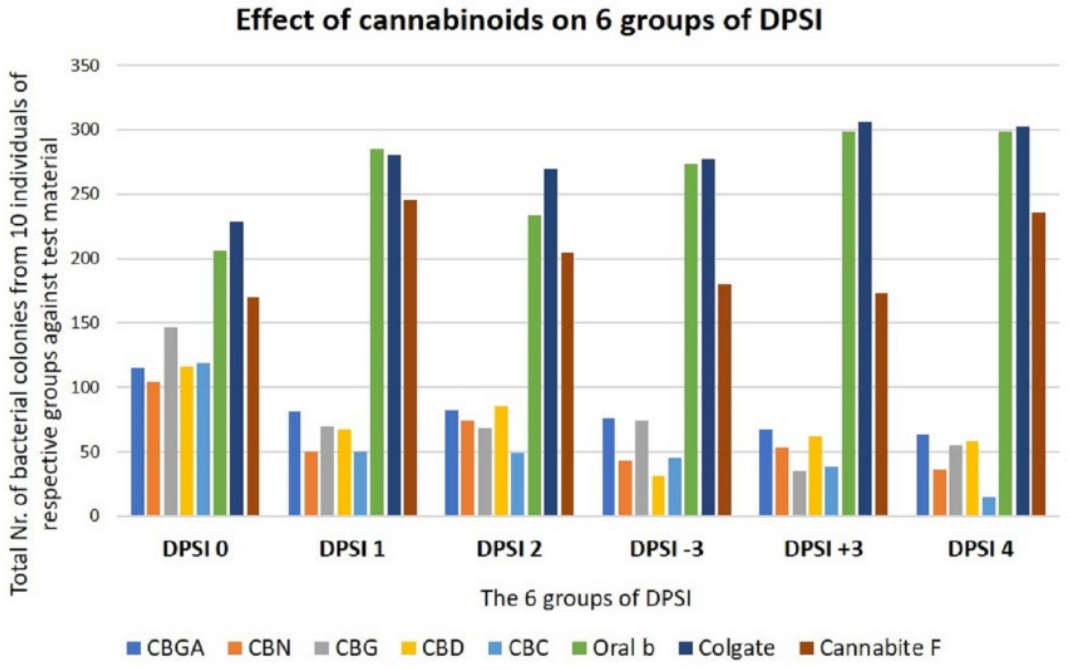


FIGURE 2: Comparison of six research groups with respect to bacterial colony count

DPSI, Dutch periodontal screening index; CBGA, cannabigerolic acid; CBN, cannabinol; CBG, cannabigerol; CBD, cannabidiol; CBC, cannabichromene and Cannabite F, formulation of pomegranate and algae.

<u>Periodontal Index</u>

DPSI 0: Perfect gum and no bleeding
DPSI 1: gingivitis (inflammation and bleeding of gum
DPSI 2: gingivitis and chalk-hardened dental plaque
DPSI (-3): (2) with bone involvement
DPSI (+3): (-3) periodontitis with gum recession
DPSI (4): (+3) w/ severe bone resorption + high tooth mobility

<u>Limitations:</u>

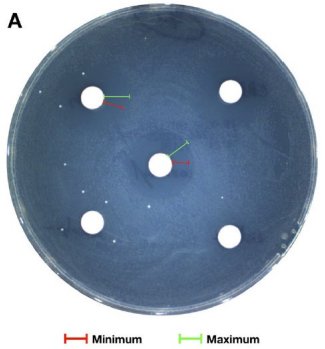
Small sample size, no statistical significance

Preliminary conclusion: Cannabinoids inhibit bacterial growth more than commercial toothpastes

Antibacterial efficacy against dental plaque bacteria of cannabinoid-infused mouthwash

Methodology

- Cannabis-infused mouthwash compared to common OTC mouthwashes and chlorhexidine
  - OTC mouthwashes (MW)
    - Product A: alcohol-containing MW w/ essential oils (thymol, eucalyptol, menthol)
    - Product B: alcohol-free MW w/ fluoride and potassium nitrate
  - CannIBite – cannabis-infused MW (CBD or CBG) (<1%)
  - Chlorhexidine (0.2%)
- Models
  - Disc diffusion model: zone of inhibition measured
  - Minimum Inhibitory Concentration measured: turbidity in test tube observed



Periodontal Disease: anti-inflammatory MOA

- Anti-inflammatory function of cannabinoids may also have add to efficacy in treating periodontal and gum disease

Cannabis-infused MW as effective as chlorhexidine

Zone of Inhibition

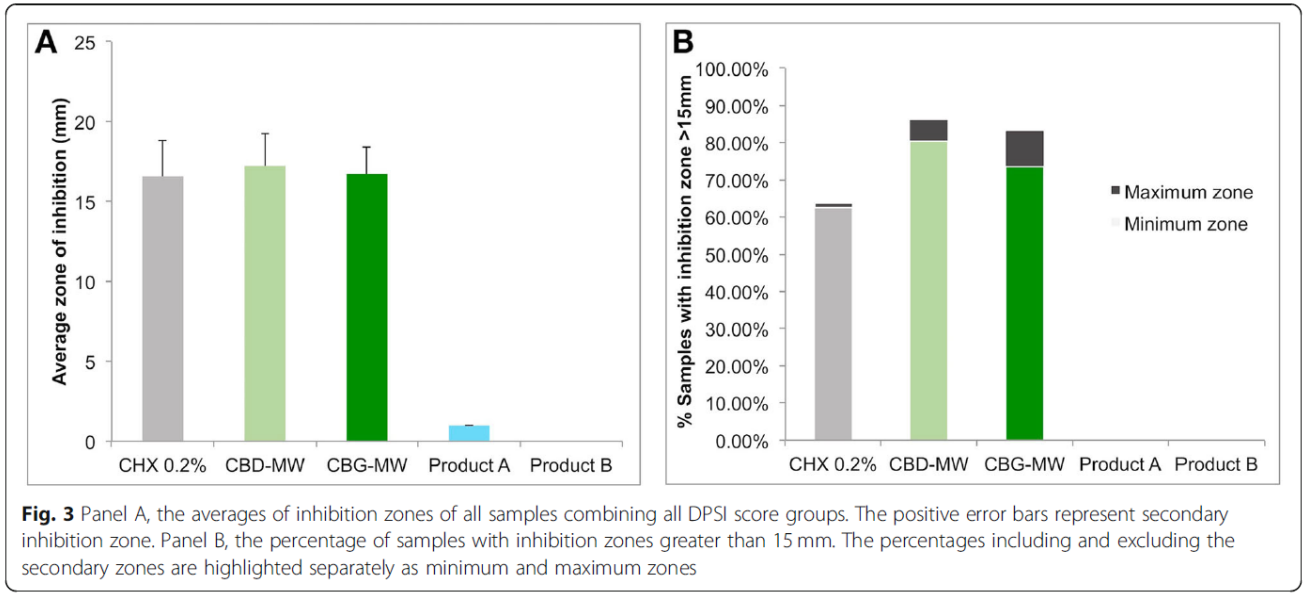
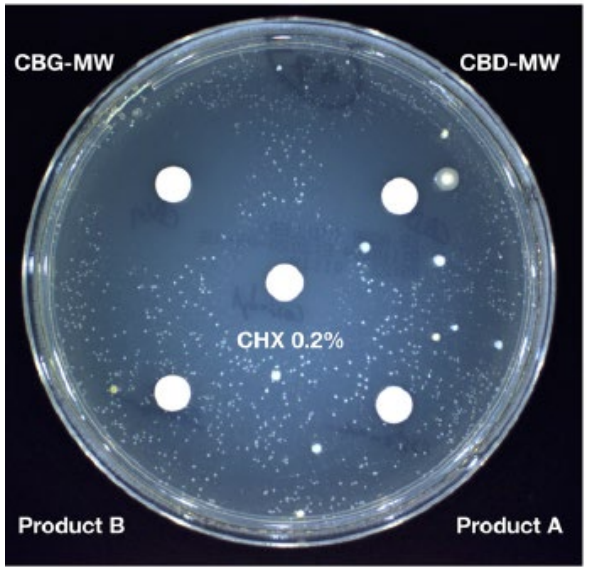


Fig. 3 Panel A, the averages of inhibition zones of all samples combining all DPSI score groups. The positive error bars represent secondary inhibition zone. Panel B, the percentage of samples with inhibition zones greater than 15 mm. The percentages including and excluding the secondary zones are highlighted separately as minimum and maximum zones



Results

- Cannabinoid MW actually more effective than chlorhexidine, but not clinically meaningful
- No differences between DPSI groups (periodontal index)
- MIC similar for chlorhexidine and cannabis MW; much more dilute than OTC products

Limitations: study not blinded; in vitro

MIC = minimum inhibitory concentration

Dental Anxiety

- Small doses of THC can be anxiolytic
- Cannabidiol: anxiolytic and anti-compulsive properties
- Clear implications for treatment/prevention of dental anxiety

Oral Cancers

- Cannabinoids: broad-based antitumor activity
- NASEM 2017 report concluded that risk-benefit ratio not favorable enough to recommend cannabinoids for cancer
- Clinical trials continue to investigate this.

Side Effects of Cannabinoids Relevant for Dentistry

Side effects of smoking cannabis

- SEs of smoking cannabis (similar to tobacco smoking)
  - Periodontal complications
  - Xerostomia
  - Leukoplakia
  - Increased risk of mouth and neck cancers

- Confounding factors in studies:
  tobacco smoking, infrequent visits to dentist, bad oral hygiene practice

- Proposed mechanisms
  - Immunosuppressive effect => yeast Candidiasis growth
  - Hydrocarbons from cannabis => energy source for Candida a
  - Xerostomia => risk factor for Candidiasis

Acute side effects - intoxication

- Symptoms of intoxication
  - Euphoria
  - Hyperactivity
  - Tachycardia
  - Paranoia
  - Delusions
  - Hallucinations

Implications of acute SEs

- Anxiety, paranoia, hyperactivity => dental anxiety
- DDI: Increased HR and other cardiorespiratory effects => epinephrine w/ local anesthetics can be potentially life-threatening
- DDI: alcohol-containing products
- Increased HR, lower BP => heart ischemia => risk of heart attack increased
- Legal implications: informed consent (esp. irreversible procedures)
- Anxiety, paranoia, psychosis => violent emergence from anesthesia

Cannabis: surgery and anesthesia

- Edibles prohibited– no solid food within 6-8 hrs of surgery (aspiration pneumonia)
- Physiological effects of marijuana increase risk of pneumonia, especially if within 1-2 hrs of anesthesia
- THC, CBD display additive prolongation of anesthetic duration
- Marijuana can increase the perception of pain after surgery (paradoxical given its general analgesic effects)
  - Cannabis users report higher pain scores, have worse sleep, and require more rescue analgesics in the immediate postoperative phase of care
  - Acute postoperative period – greater pain perception
  - Still useful in chronic pain treatment

Anesthesia – special considerations

- Chronic use of marijuana:
  - larger doses of anesthesia generally required
    - Regular marijuana users require over 3x as much propofol to achieve adequate anesthesia
    - Other evidence in animal models for other anesthetics (variable response)
  - Potential upper airway obstruction, chronic cough, bronchitis, emphysema
- Acute use of marijuana:
  - 5x risk of M.I. in the first hour following use
    - Increased cardiac output and myocardial oxygen demand
    - catecholamine levels, and carboxyhemoglobin
    - postural hypotension

How to treat marijuana users as dentists

- Chronic users:
  - Ask last use, how much they use, and dose
  - Assess for acute intoxication
    - Assess for symptoms of anxiety, paranoia, or psychosis
  - For MJ smokers, evaluate for surgery in similar fashion as tobacco smoker
    - One report recommended use of dexamethasone
  - Evaluate for other cardiovascular risk factors
  - May require higher dose for induction
    - depends on cannabinoid and anesthetic; evidence stronger for propofol
- Acute intoxication
  - Delay 24 hrs or at least 1-2 hrs
    - Risk of MI subsides after ~1 hr
  - Delay until after tachycardia and hypotension resolve

How to recognize patient may be marijuana user (acute and chronic SEs)

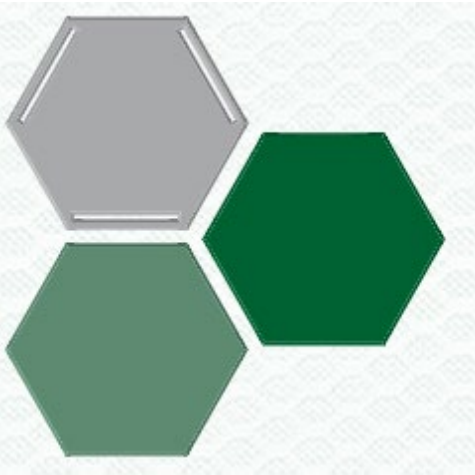
- Anxiety
- Reduced levels of coordination
- Bloodshot eyes
- Increased heart rate and blood pressure
- Sore throat
- Trouble concentrating and paying attention
- Smell of marijuana
- Infections such as sinusitis, bronchitis, and asthma in heavy users
- Irritation of the airways causing narrowing or spasms
- Possibly weakening of the immune system

FAQ – Vaping and dental caries risk

- Vaping pen ingredients:
  - water, food grade flavoring, a choice of nicotine levels, cannabis (THC, CBD), propylene glycol (PG) or vegetable glycerin
  - Flavoring agents sometimes added to cannabis when vaping

- Vaping sweet e-cigarettes can increase the risk of dental cavities
  - Ingredients have similar properties to high-sucrose, gelatinous candies and acidic drinks
  - Ingredients also cause hyposalivation, increasing risk of dental caries
  - Flavors that are sweet or low pH can increase biofilm formation when exposed to caries-producing Streptococcus mutan

Thank You!



Contact:

James.odon@gmail.com

https://pharmaconsultantinc.com/