Pain and Inflammation: Innovations

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5 – Loxin (Boswellia Serratia Extract)[1-5]

- Mechanism of Action
  - Inhibit 5-lipoxygenase and reduces leukotriene synthesis
  - Inhibits leukocyte elastase
- Dose
  - 100-250mg daily by mouth
- Safety
  - Often used to treat pain and inflammation usually associated with arthritis
  - Well-tolerated orally

5 – Loxin (Boswellia Serratia Extract)[1-5]

- Side Effects
  - Diarrhea
  - Nausea
  - Abdominal pain
  - Heartburn
  - Itching
  - Headache
  - Edema
  - General Weakness

- Drug Interactions: dose adjustment might need to be made
  - CYP1A2 substrates
  - CYP2C19 substrates
  - CYP2C9 substrates
  - CYP2D6 substrates
  - CYP3A4 substrates
  - Immunosuppresants

Cat Claw[6-8]

- Mechanism of Action
  - Antinociceptive effects through interaction with 5-HT2 receptors
  - Used primarily for osteoarthritis and rheumatoid arthritis
- Dose
  - 100mg by mouth daily
    - Containing freeze-dried aqueous cat's claw extract (uncaria gluianesis)
- Safety
  - Safe when used short term (seen used up to 4 weeks
  - Well tolerated

Cat Claw[6-8]

- Side Effects
  - Headache
  - Fatigue
  - Insomnia
  - Abdominal pain
- Drug Interactions: use the following with caution
  - Anticoagulant/Antiplatelet drugs
  - Antihypertensive drugs
  - Calcium channel blockers
  - Protease inhibitors

Egg Shell Membrane[9-11]

- Mechanism of Action
  - Extracted yolk immunoglobulin (IgY can be used in humans to provide passive immunity and help treat the specific conditions for which the hens were immunized against
  - Contains naturally occurring glycosaminoglycans and proteins essential for maintaining healthy joint and connective tissues
- Dose
  - 500mg
- Safety
  - Well tolerated

Egg Shell Membrane[9-11]

- Side Effects
  - Diarrhea
  - Gas
  - Bloating
- Drug interactions
  - None known

UC-II[12-15]

- Also known as type II collagen
- Mechanism of Action
  - Potential autoantigen
  - Initiates and maintains the immune response
  - Suppressor CD8+T cells can be stimulated in a trigger-specific and effector-nonspecific way by contact with type II collagen in the joint
- Dose
  - 40mg Daily

UC-II[12-15]

- Side Effects
  - Stomach upset
  - Vomiting
  - Anorexia
  - Mouth ulcers
  - Nausea
  - Burping
- Drug interactions
  - None known

Proteolytic Enzymes

- Common proteolytic enzymes: pepsin, bromelain, papain
- Mechanism of Action
  - Digest protein by aiding in the digestion process, breaking it down into amino acids
- Safety
  - Generally safe

L-Theanine

- Major amino acid found in green tea
- Mechanism of Action
  - Increased activity in the alpha frequency band
- Side Effects
  - Hypotension
- Dosing
  - ADHD-specific dosing not available
  - Used at 200mg-400mg/day for anxiety
- Drug Interactions
  - Additive hypotensive and stimulant actions

Evidence for the use of 5-HTP

- Over 100 clinical trials have studied the use of 5-HTP in depression
- A Cochrane Review was conducted in 2002[55]
  - 5-HTP was found to have a magnitude of effect similar to SSRIs
  - A number of cases of fatal eosinophila myalgia syndrome (EMS) have been associated with the use of tryptophan
  - Despite apparent clinical efficacy, the link between cases of EMS have not yet been determined

Co-Enzyme Q10

- Key component of cellular respiratory chain
- Statins disrupt krebs cycle and deplete levels of CoQ10
- Preliminary evidence that common side effects of myopathies and liver inflammation are in part due to CoQ10 depletion
- Some patients supplement with CoQ10 to alleviate symptoms
- Used in various neurological disease treatments, cardiovascular, and diabetes
- Dose 100-300mg day

Omega 3 Fatty Acids

Fish Are Your Friends

Capsicum[16-17]

- Its constituent is capsaicin
- Mechanism of Action
  - Activator of nociceptors, cutaneous peripheral receptive endings of primary sensory neurons (unmyelinated C-fibers) activated by noxious stimuli
  - The neurons are desensitized
  - Capsaicin induces sensitization to C-fibers that are mechano- and heat-insensitive and inhibits desensitization of C-fibers that are mechano- and heat-responsive
  - Capsaicin suppresses histamine-induced itching in healthy skin. It has been suggested that capsaicin-sensitive nerves are involved in histamine release

Capsicum[16-17]

- Dose
  - Cream has been used for pain at the local site
  - 0.025% to 0.075% cream
  - Take 4 to 6 weeks to work
- Safety
  - Safe when used orally and topically for short-term periods

Capsicum[16-17]

- Adverse Effects
  - GI irritation
  - Throat irritation
  - Flatulence
  - Diarrhea
  - Dyspepsia
- Drug Interactions: use the following with caution
  - ACE inhibitors
  - Anticoagulant/Antiplatelet drugs
  - Antidiabetic drug
  - Antihypertensive drugs
  - Aspirin

Ginger[19-20]

- Mechanism of Action
  - Inhibitory effect of 6-shogaol on the release of substance P
  - Inhibit cyclooxygenase (COX) and lipoxygenase pathways, and leukotrienes
- Dose
  - Ginger extract 1000mg daily
- Safety
  - Safe orally when used appropriately
  - Well-tolerated

Ginger[19-20]

- Side Effects
  - Abdominal discomfort
  - Heartburn
  - Diarrhea
- Drug Interactions: use with caution with these medications (dose adjustments may be necessary)
  - Anticoagulant/Antiplatelet drug
  - Nifedipine – major interaction
    - Do not take – inhibits platelet aggregation significantly

Feverfew[21-23]

- Mechanism of Action
  - Inhibit serum proteases and leukotrienes
  - Blocks prostaglandin synthesis by inhibiting phospholipase, which prevents the release of arachidonic acid
- Dose
  - 50-150 by mouth once daily
- Safety
  - Well tolerated when used appropriately and short-term

Feverfew[21-23]

- Adverse Effects
  - Skin rash (topical)
  - Palpitations
  - Heartburn
  - Nausea
  - Diarrhea
  - Constipation
  - Bloating
  - Flatulence

- Drug Interactions: use with caution in combination with the following medications
  - Anticoagulant/antiplatelet drugs
  - Cytochrome P450 substrates

Turmeric

- Also known as curcumin
- Mechanism of Action
  - Inhibits transient receptor potential vanilloid 1 (TRPV1)-mediated pain hypersensitivity
  - Inhibits NF-kB activation
  - Inhibits cyclooxygenase-2 (COX-2), prostaglandins, leukotrienes, and other cytokines involved in pro-inflammatory signaling pathways
- Dose
  - 500mg twice daily (OA)
  - 400mg three times daily (RA)
- Safety
  - Generally well tolerated

Turmeric

- Side Effects
  - Dyspepsia
  - Nausea
  - Vomiting
  - Diarrhea
  - GI upset
- Drug Interactions: use with caution with these medications
  - Antiplatelet/anticoagulant drugs
  - Antidiabetic drugs

Devil's Claw

- Orally, used for arteriosclerosis, osteoarthritis, rheumatoid arthritis, gout, myalgia, fibrositis, lumbago, tendonitis, pleuritic chest pain, gastrointestinal (GI) upset or dyspepsia, fever, and migraine headache.
- Well-tolerated when used daily for up to a year
- Anti-inflammatory mode of action

Dosing

- Osteoarthritis, a specific powdered devil's claw root product (Harpadol, Arkopharm) dosed at 2.6 grams/day
- Back pain, a specific devil's claw extract (Doloteffin, Ardeypharm) providing 50-100 mg harpagoside daily has been used

Devil's Claw

- Diarrhea, occurring in approximately 8% of patients in one study
- Other gastrointestinal complaints include nausea, vomiting, and abdominal pain.
- Allergic skin reactions
- Dysmenorrhea and hemodynamic instability
- Report of throbbing frontal headache, tinnitus, anorexia, and loss of taste associated with devil's claw

Drug Interactions

- CYTOCHROME P450 2C19 (CYP2C19) SUBSTRATES
- CYTOCHROME P450 2C9 (CYP2C9) SUBSTRATES
- CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES
- H2-BLOCKERS
- **Check with RPH before using with drug list**

MSM

- Orally and topically, MSM is used for:
  - chronic pain
  - osteoarthritis,
  - joint inflammation
  - rheumatoid arthritis
  - bursitis, tendinitis

MSM

- MSM in doses of 2.6 to 6 grams/day has been used safely in studies lasting up to 12 weeks
- MSM is a naturally occurring compound found in green plants
- MSM is an odorless metabolite of dimethylsulfoxide (DMSO).
- MSM is primarily used for osteoarthritis. Preliminary research suggests MSM might inhibit degenerative changes in joints in animal models of osteoarthritis

MSM

- No Drug Interactions
- Nausea, diarrhea, bloating, headache, fatigue, insomnia, and difficulty concentrating in clinical studies
  - These side effects do not appear to occur more often than with placebo
  - MSM has also caused pruritus and increased allergy symptoms in some patients

D-Phenylalanine

- Essential Amino Acid- Milk and Meat
- Blocks the degredation of Enkephalins
- L-Phenylalanine found in food
- D-Phenylalanine protects endorphins
- Upregulates endogenous analgesic system
- No tolerance
- Benefit over time
- Contraindicated in Phenylketonuria, HTN, cancer, Parkinson, TD, MAO-I

Phenylalanine

- 4 weeks to efficacy
- D form 500mg BID to TID

Drug Interactions

- Antidepressant agents: Hypomania theoretically may occur
- Antidepressant agents, monoamine oxidase inhibitors (MAOIs
- Antipsychotic agents: Tardive dyskinesia worsened in severity
- Baclofen: Dietary supplements of phenylalanine theoretically may inhibit absorption of baclofen
- Cardiovascular agents: Antihypertensive drugs theoretically may be less effective, given that L-phenylalanine and D-phenylalanine have tyrosine as a metabolite

Drug Interactions

- Clobetasol: Vitiligo improved in 90.9% of patients with treatment with the combination of oral L-phenylalanine 100mg/kg daily, topical phenylalanine as a 10% gel, sunlight or irradiation with ultraviolet A, and nightly clobetasol propionate 0.025% in a case series
- Cytochrome P450 metabolized agents
- Immunomodulators: Interactions hypothetically may occur, given that L-phenylalanine's metabolite, phenylethylamine may inhibit synthesis of antibodies
- Levodopa: Tremor, rigidity, weakness, and drowsiness developed with ingestion

Hypericum perforatum (St. John's Wort)

- Perennial herb native to Europe, North Africa, and western Asia
- Originally documented by Hippocrates
- "Arnica for the nerves"
- The traditional way to take SJW was as herbal tea.

St. John's Wort: Traditional Uses

- Depression
- Dysthymia
- Anxiety
- Mood disturbances associated with PMS/Menopause
- Attention deficit-hyperactivity disorder (ADHD)
- Obsessive-compulsive disorder (OCD)
- Seasonal affective disorder (SAD)
- Exhaustion
- Smoking cessation

St. John's Wort: Traditional Uses

- Fibromyalgia
- Chronic fatigue syndrome (CFS)
- Menopausal symptoms
- Headache
- Neuralgia
- Sciatica
- Bruises and abrasions
- Inflammation
- Burns and wound healing
- Hemorrhoids

St. John's Wort: Active Constituents

- Two constituents play a significant role
  - Hypericin and Hyperforin
- Hypericin was formerly thought to be the principal component
- Now understood that hyperforin, adhyperforin, and several other related compounds are the primary active constituents
- Small amounts of melatonin present as well

St. John's Wort: Mechanism of Action

- Modulate serotonin, dopamine, and norepinephrine and may inhibit reuptake of these neurotransmitters
- Act as a serotonergic 5-HT3 and 5-HT4 receptor antagonist and down-regulate beta-adrenergic, and serotonergic 5-HT1 and 5-HT2.
- Cortisol stimulation in a dose-dependent manner
- Hyperforin also inhibits synaptosomal uptake GABA.
- nhibits catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO).

St. John's Wort: Clinical Use

- St. John's wort is official in the national pharmacopeias of Czechoslovakia, France, Poland, Romania, and Russia
- In Germany, SJW is listed in the *German Drug Codex*, approved as a medicine in the Commission E monographs, and licensed as a standard medicinal tea infusion
- United States Pharmacopeia Drug Information division issued a therapeutic monograph and consumer information bulletin stating that the USP Advisory Panels do not recommend or support the use of SJW
- Over 40 human clinical trials, including 4 meta-analyses, including thousands of subjects

St. John's Wort: Depression

- St. John's wort extracts are more effective than placebo in mild-moderate depression
- As effective as low-dose tricyclic antidepressants, and fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil).
- SJW improves mood, decreases anxiety and somatic symptoms, and decreases insomni
- Short-term response rates to St. John's wort appear to between 65% and 100%
- Some evidence for depression in children 6 to 16 years old

St. John's Wort: Mood Disorders

- St. John's wort plus black cohosh extract significantly reduces menopausal symptoms in women who have pronounced psychological symptoms.
- Improves PMS symptoms by approximately 50% in some women
- Seasonal affective disorder – reduces anxiety, decreased libido, and sleep disturbances
  - It is useful alone or in combination with light therapy

SJW: Dosing

- Standardized to 0.3-0.5% hypericin and/or 3-5% hyperforin per dose
- Dosage: 300mg (standardized extract) three times a day
- Side effects can include insomnia, vivid dreams, restlessness, anxiety, agitation, irritability, gastrointestinal (GI) discomfort, diarrhea, fatigue, dry mouth, dizziness, and headache
- May induce hypomania in depressed patients and mania in patients with bipolar disorder

SJW: Cautions

- St. John's wort is a potent inducer of cytochrome P450.
- Hyperforin constituent is responsible for interactions.
- Hypericin does not seem to significantly affect drug metabolism.
- Increases induction activity of CYP3A4 by 98%
  - Greater in females than males
- Also induces CYP2C9 and CYP1A2

SJW and Drug Metabolism

- Cyclosporine
- Indinavir
- Amitriptyline
- Oral contraceptives
- Reserpine
- Digoxin
- Narcotics
- Barbiturates

S-adenosylmethionine (SAMe)

- Used by over 1 million Europeans
- 3 decades of use
- Approved Rx in
  - Spain
  - Russia
  - Germany
  - Italy
- Outsells Prozac in Italy despite more reimbursement

S-adenosylmethionine (SAMe)

- Distributed throughout virtually all body tissues and fluids.
- Concentrations are highest in childhood and decrease with age.
- Plays an essential role in 100s of biochemical reactions
  - Transmethylation
  - Transsulfuration
  - Aminopropylation
- SAMe contributes to the synthesis, activation and/or metabolism of hormones, neurotransmitters, nucleic acids, proteins, phospholipids, and some drugs

Methyltransferase Reactions

- Shift the 'active' methyl group of SAMe to a wide variety of methyl 'acceptor' molecules, including biogenic amines, fatty acids and phospholipids, proteins, nucleic acids, polysaccharides and porphyrins
- Considered the most important methyl group donor in mammalian tissue
- Contributes directly to homocysteine metabolism and tightly tied to B vitamin status

Transsulfuration Reactions

- S-Adenosylhomocysteine (SAH) yields homocysteine, then converted to cysteine and glutathione
- SAMe provides the sulphur for the important cartilage building blocks.
- Donates cysteine for glutathione production in the liver.
- Shown to increase GSH levels

SAMe: Depression

- SAMe has been administered parenterally, IM, ot orally
- All routes have been shown to improve symptoms of depression
- As effective as tricyclic antidepressants in trials lasting up to 42 days
- Parenteral SAMe has been used successfully in combination with oral tricyclics to speed the onset of antidepressant action

SAMe: Depression

- Slowing of methylation or genetic predisposition to methylation could be a key to depression
- Protein methylation --- activation of receptors
  - ↑ receptors
  - ↑ level neurotransmitters
- SAMe boosts phospholipid metabolism
  - ↑ phosphatidylersine and choline

SAMe: Depression

- CSF Marker Changes
- ↑ serotonin
- ↑ dopamine

SAMe: Osteoarthritis

- Multiple clinical trials show that taking SAMe orally is superior to placebo and comparable to NSAIDs, including the COX-2 inhibitor celecoxib (Celebrex), for decreasing symptoms associated with osteoarthritis.
- Has anti-inflammatory and analgesic properties
- SAMe is associated with fewer adverse effects than NSAIDs and is comparable in reducing pain and improving functional limitation
- Significant symptom relief may require up to 30 days of treatment.

SAMe: Other

- Detoxification
- Liver cholestasis
- Fibromyalgia

SAMe Therapeutics

- Dosage Range: 200-1,600mg daily

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Medical Marijuana

Objectives

- Understand contributions of animal and human research to understanding role of endocannabinoid receptors in addiction
- Identify regions of brain where endocannabinoid receptors are most common
- Understand interactions between endocannabinoid receptors and other neurotransmitter systems
- Review the various clinical use for medical marijuana

What Is medical marijuana?[10]

- "Medical Marijuana refers to using the whole unprocessed marijuana plant or its basic extracts to treat a disease or symptom"
- The FDA has not recognized or approved the marijuana plant as medicine
- The chemicals in marijuana are called cannabinoids
  - There are two FDA-approved medication that contain cannabinoids

Background[1]

- Marijuana is the female flowers and dried leaves of the hemp plant called cannabis sativa
- 23 states and the District of Columbia have legalized medical marijuana
- Cannabis is the plant that grows marijuana
- All marijuana can be considered medical-grade since it all has some therapeutic effect

Background[4]

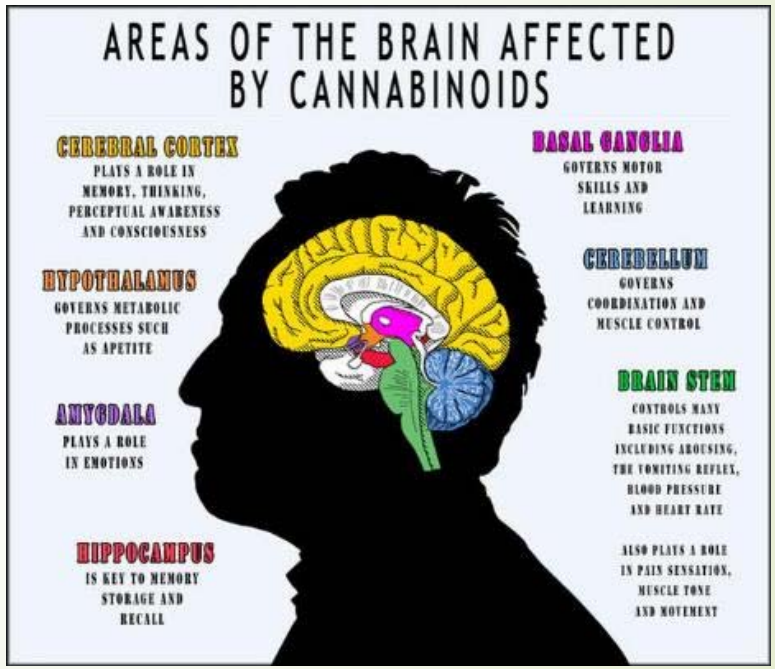
- The potency of marijuana varies from strain to strain
  - As low as 2-3% THC
  - As high as 30% THC
- Higher potency indicates that the patient will need to consume less to receive the same outcome of that with a lower dose and higher quantity

What are cannabinoids?[10]

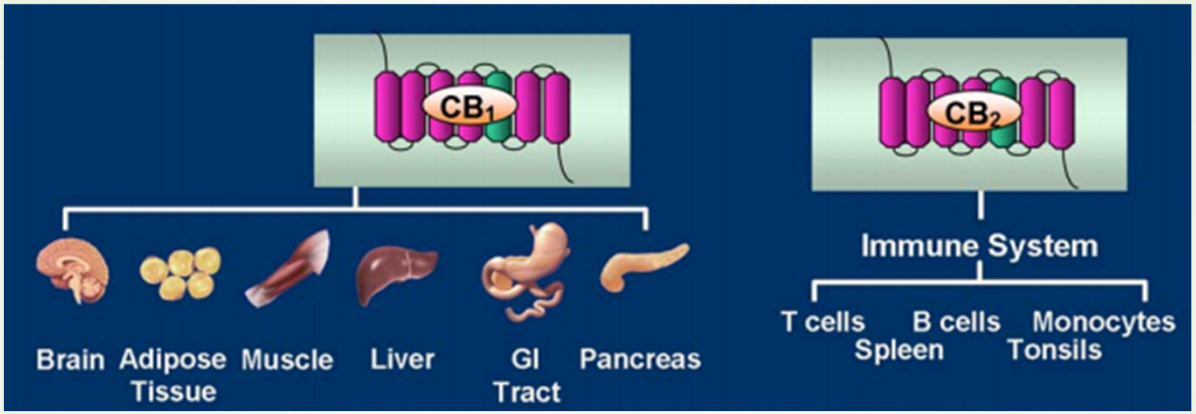
- Cannabinoids are chemicals that are related to the commonly known ingredient in marijuana known as THC (delta-9-tetrahydrocannabinol)
- Another cannabinoid of interest is CBD
- There are over 100 other cannabinoids other than THC that is found in marijuana
- Cannabinoids are similar to flavinoids that are found in chocolate

What are cannabinoids?[10]

- The body produces its own cannabinoids that help to regulate the following:
  - Pleasure
  - Memory
  - Thinking
  - Concentration
  - Body movement
  - Awareness of Time
  - Appetite
  - Pain
  - Senses – taste, touch, smell, hearing, and sight



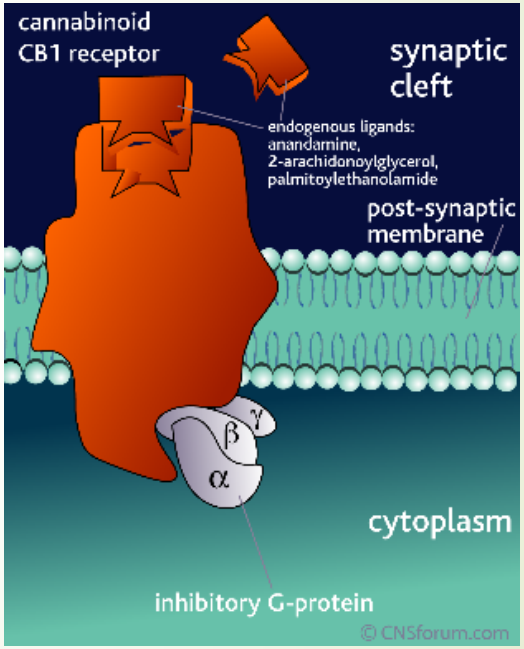
Cannabinoid Receptors[21-25]



- Receptors are CB_1 and CB_2
  - CB_1 - mostly expressed in the brain, but also found in adipose tissue, liver, muscle, GI tract, and in reproductive and cardiovascular tissues
  - CB_2 – mostly expressed in immune cells
- G-protein coupled receptors

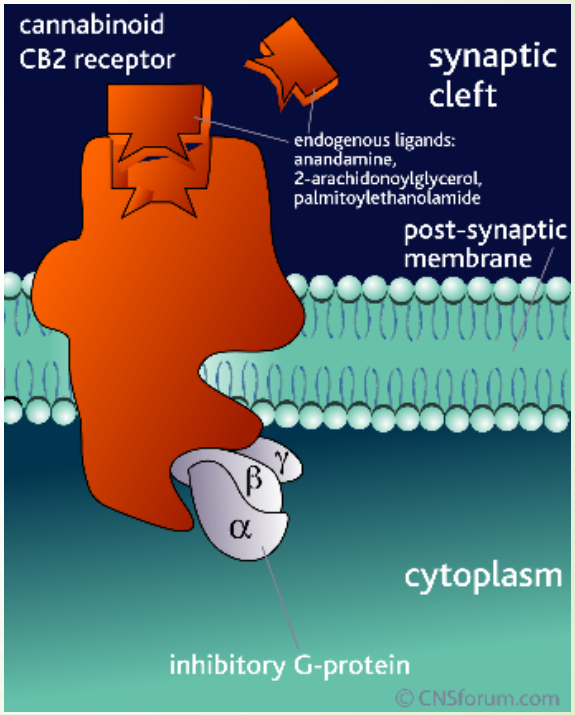
CB_1 Receptor[28]

- Effects of CB_1 are neuromodulatory
- Affect the following neurotransmitters:
  - Acetylcholine, norepinephrine, dopamine, serotonin, aminiobutyric acid, glutamate, and D-aspartate



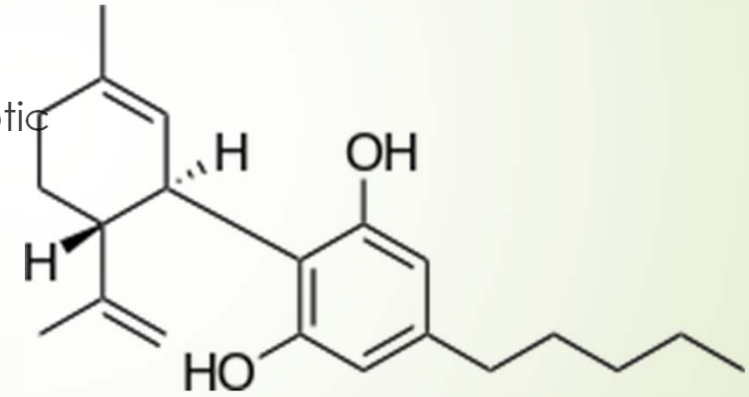
CB_2 Receptor[28]

- Present mainly on peripheral tissues and central immune cells
- Activation of this receptor leads to:
  - Immunosuppression
  - Anti-inflammatory effects
  - Anti-nociceptive effects



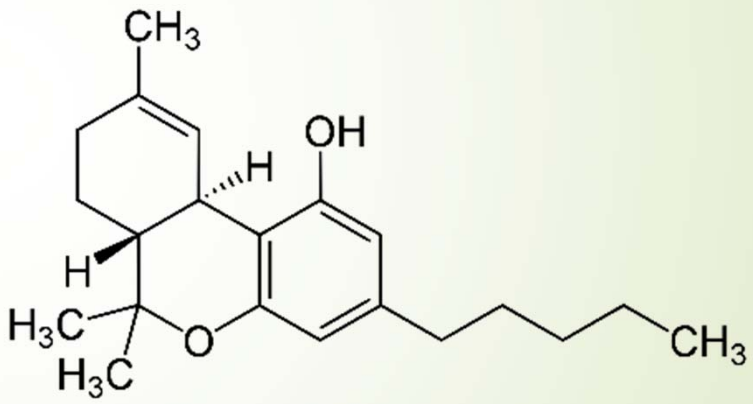
What is CBD?[10]

- Cannabidiol (CBD) is a cannabinoid, but it does not affect mind or behavior
- It is useful in reducing pain and inflammation, controlling epileptic seizures, and possibly treating mental illness and addictions



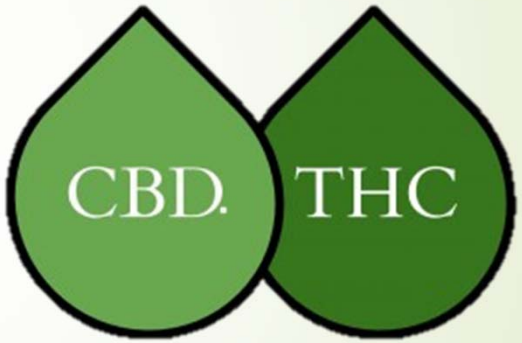
What is THC?[10,11,31]

- THC is short for Δ9-tetrahydrocannabinol
- It is a potent antioxidant with neuroprotective properties
- THC is a partial agonist for the CB1 receptor
- CB1 receptors regulate the release of other neurotransmitters



What is THC?[10,11]

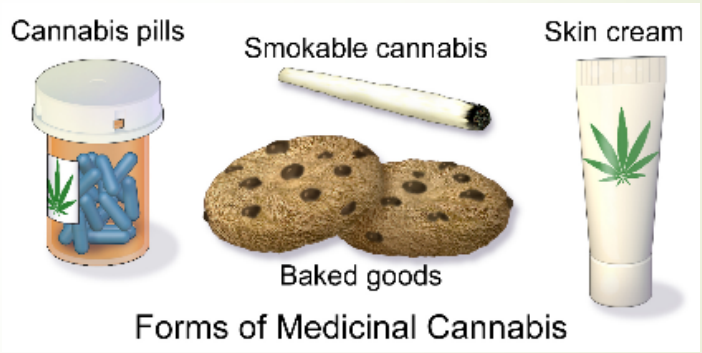
- THC increases appetite and reduces nausea
- THC may also decrease pain, inflammation, and muscle control problems
- The FDA has approved the use of THC for appetite and nausea reduction purposes
  - Dronabinol



Pharmacokinetics & Pharmacodynamics

Forms of medical marijuana[2]

- Smoked – most common form
- Capsules
- Vaporization
- Edible form
- Suppositories
- Liquid to drink



Pharmacology of Cannabis

- Cannabinoids are highly lipophilic and lipoprotein bound
- Volume of distribution (Vd) = 10 L/kg
  - Blood concentrations are therefore not directly related to the drug effect
- The release from the lipid stores along with enterohepatic recirculation accounts for retention of THC
  - Terminal half-life is > 4 days in frequent users

Pharmacology of Cannabis

- Urine THC can be detected for days after use
- Passive inhalation – requires very high concentrations of smoke in a small enclosed area
  - Very unlikely

Onset and duration of cannabis

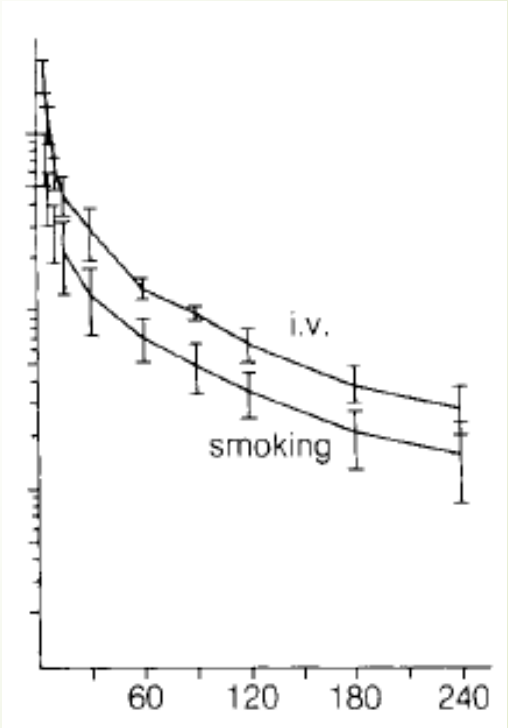
- Physical and psychosocial effects commence within minutes after use
  - Usually within 15 minutes
  - Peak effects occur within 30 minutes to 60 minutes post-smoking and last 2-4 hours
- Psychosocial effects can stay for up to 4 to 8 hours depending upon route of administration
  - Oral has a slower onset, but longer duration

Psychosocial effects

- Effects do not depend on blood concentration
  - Depends partially on the dose
- Effects are dose-dependent and route-dependent
  - Lower dose effects: euphoria, relaxation, wide range from exhilaration to introspection, distortion of time and some visual hallucinations, memory distortions (especially short-term memory), hunger
  - Higher dose effects: anxiety, tension, anger, confusion, hallucinations, paranoia, and panic attacks

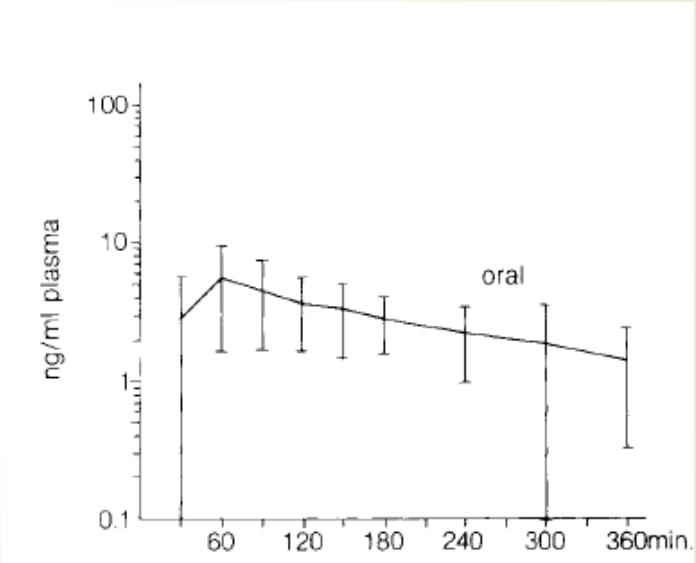
Pharmacokinetics of smoking THC[31]

- Bioavailability: 10-25%
  - 50% of the THC content is delivered into smoke
  - 50% of smoke is exhaled again
    - 60% of inhaled smoke may be metabolized by the lung
- Peak concentrations are reached within minutes
- $T_{1/2}$ distribution: 0.5hr
- $T_{1/2}$ elimination: 30hr
- Smoking THC mimics IV



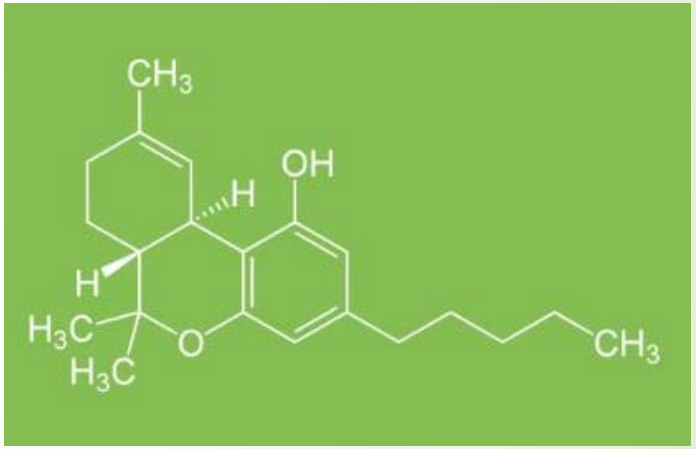
Pharmacokinetics of oral THC[31]

- Bioavailability: 5-20%
  - Usually 1/3 of that smoked due to gastric degradation and extensive first pass metabolism effects
  - High patient variability
    - Can lead to increased toxicities because delayed effect
- Multiple low peak concentrations reached in 1-3hr
- $T_{1/2}$ absorption: 0.8hr
- $T_{1/2}$ distribution: 3.8hr
- $T_{1/2}$ elimination: 25hr



Dose of THC[31]

- Effective dosing of THC
  - Low dose: <7 mg
  - Medium dose: 7-18mg
  - High dose: >18mg
- Tolerance to THC exists via the down regulation of the CB1 receptors
  - High tolerance occurs with chronic use
  - Low tolerance occurs with intermittent use

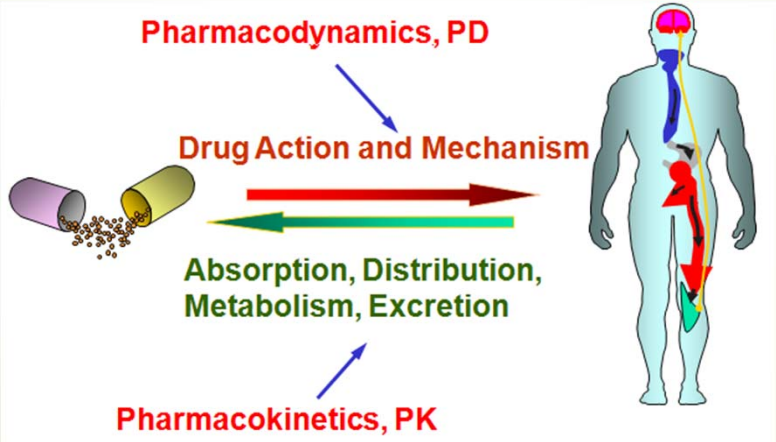


Vaporization

- Cannabinoids vaporize at a temperature lower than combustion
- Results in lower percent of noxious chemicals

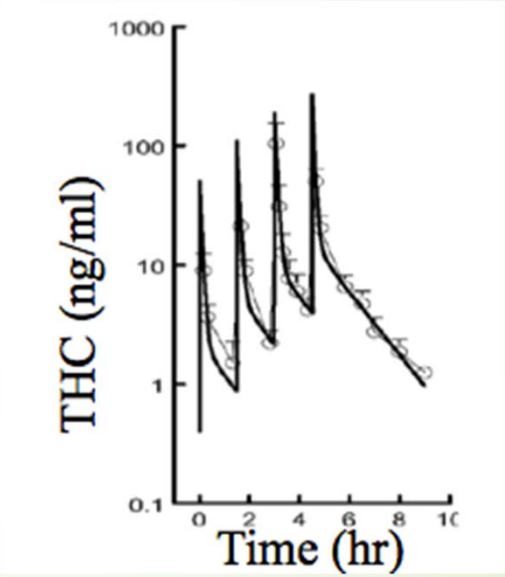
Pharmacodynamics of THC[32]

- Elevation in heart rate: average >19bpm
- Increase in subjective feeling high
- Decrease in subjective alertness
- Increase in motor instability
  - Body sway

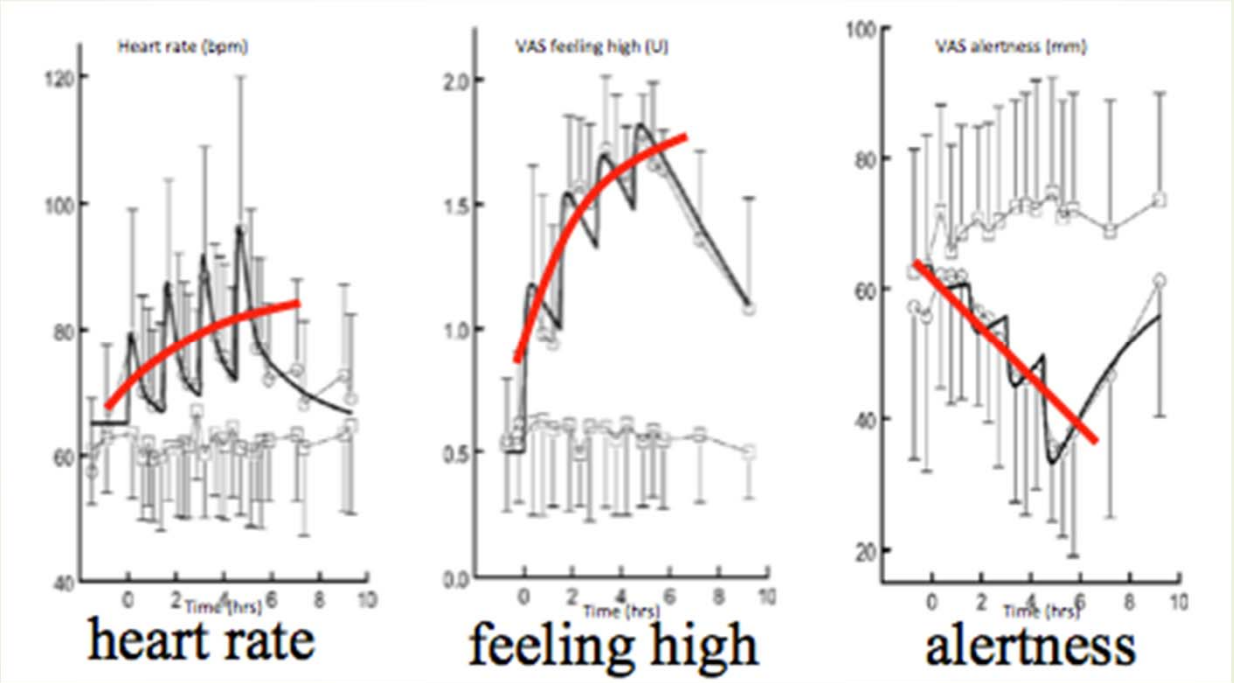


PK/PD Model of THC[32]

- In study by Zuuman et al, subjects were given increasing doses (2, 4, 6, 8mg) of THC via vaporizer at 1.5hr intervals



PK/PD Model of THC[32]



Medical cannabis Impact on Hormones

- Males:
  - Decreases luteinizing hormone (LH)
  - Decreases follicle stimulating hormone (FSH)
  - Decreased Prolactin
  - Decreased growth hormone (GH)
- Females: More sensitive than males to THC effects
  - Higher estrogen levels

Marijuana effects on the brain

Marijuana effects

- Hypothalamus: increased appetite
- Brain stem: nausea relief, lowered blood pressure, drowsiness, decreased pain, decreased spasticity, and decreased tremor.
- Hippocampus: memory impairment

Marijuana effects

- Cerebral cortex: altered consciousness, perceptual distortions, memory impairment, delusions, hallucinations
- Cerebellum: loss of coordination
- Amygdala: changes in anxiety, pain attacks, lowered traumatic memories, decreased hostility

Uses of medical marijuana

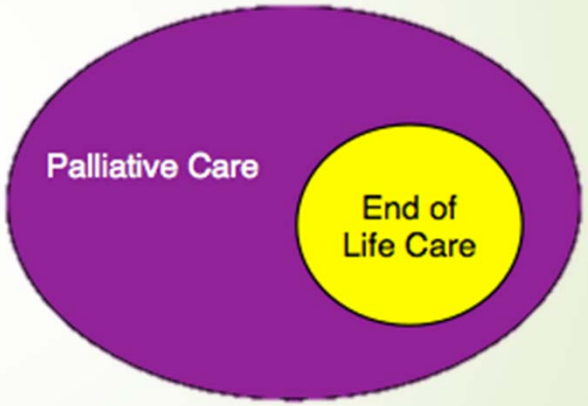
Qualifying Medical Conditions[3]

- Alzheimer's Disease
- Amyotrophic lateral sclerosis (ALS)
- Cachexia C
- Crohn's Disease
- Severe and chronic pain
- Severe and persistent muscle spasms
  - Ex. MS

- Anxiety
- Cancer
- Glaucoma
- HIV
- Hepatitis C
- Acquired immunodeficiency syndrome
- Seizures, epilepsy

Medical Marijuana and palliative care

- Medical marijuana is centered on palliative care—improving quality life of patients and families in order to mitigate suffering

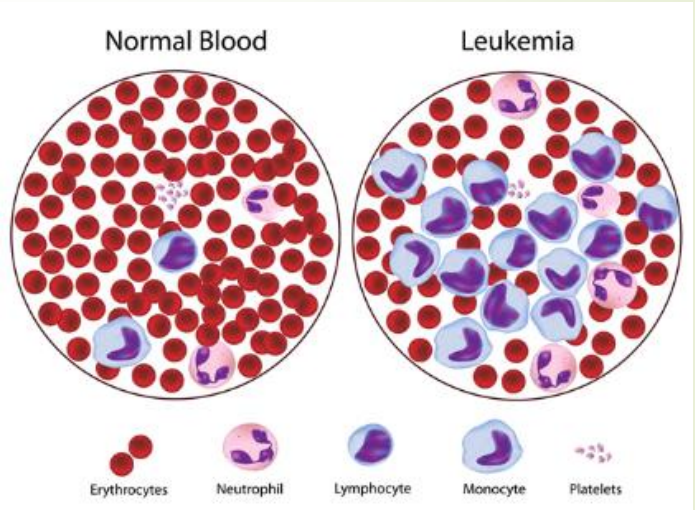


Children[13]

- Children are not the first age group to be considered for medical marijuana
- A use of medical marijuana in children is the treatment of severe seizures
  - The oil of the cannabis is extracted and used for treatment
- The long-term effects of early marijuana use in children is not fully understood

Leukemia

- Cannabidiol (CBD) has anticancer properties
  - Both as a single agent and in combination
- Mechanism of action is unknown
  - Know that it involves intracellular signaling pathways and underpin cellular proliferation, survival, and death



hIV/AiDs

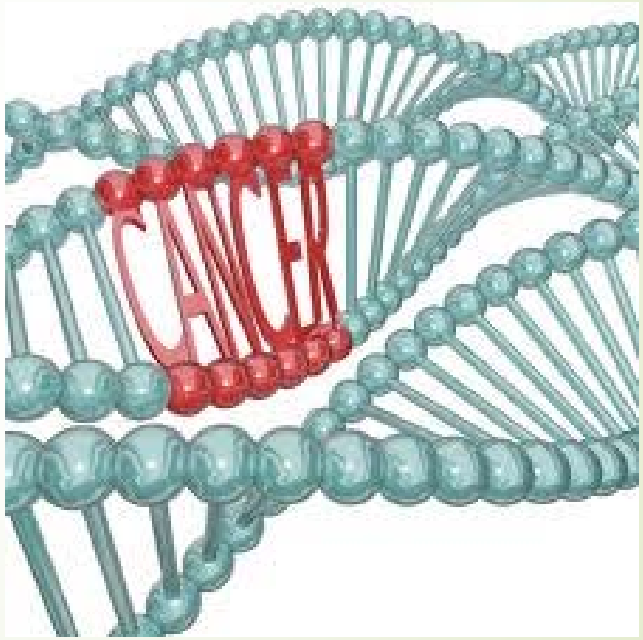
- Marijuana used as an appetite enhancer and pain-relieving medication in HIV-infected patients
- Also can be used for the following in these patients
  - Sleep/relaxation
  - Prevent nausea/vomiting
  - Pain
  - Anxiety/depression
  - Stimulation/energy

HIV/AIDS[6]

- Study assessed if smoked cannabis is effective as an analgesic in HIV-associated distal sensory polyneuropathy
- It was found that pain relief was greater with cannabis compared to the placebo

Cancer[7]

- Benefits
  - Inhibits chemotherapy-induced nausea and vomiting
  - Appetite stimulation
  - Pain inhibition
  - Inhibit tumor growth
- Has favorable drug-safety profile and does not produce the conventional side effects of chemotherapy drugs

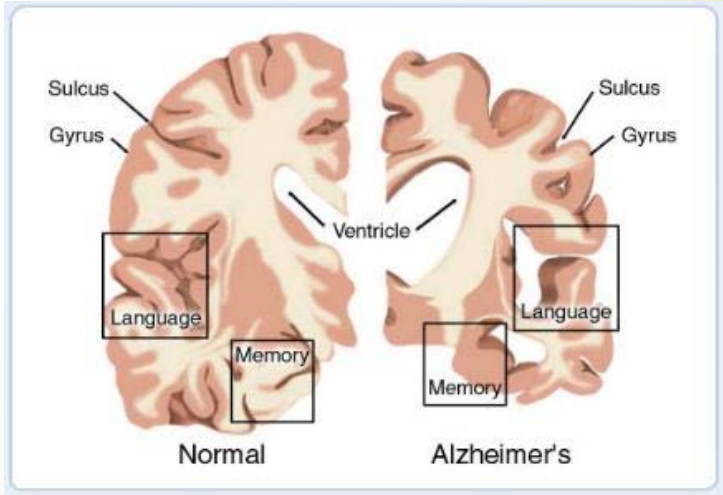


Migraines[8]

- Medical marijuana has ability to:
  - Modulate serotonergic receptor subtypes
  - Inhibit glutamatergic-mediated toxicities
  - Provides anti-inflammatory activity
  - Provides acute symptomatic and chronic preventative relief

Alzheimer's Disease[11]

- Seen that low doses of THC reduce the production of amyloid beta
- Low level of THC also help to enhance mitochondrial function, which helps to provide energy, transmit neuron signals, and maintain a healthy brain



Amyotrophic Lateral Sclerosis (ALS)[15, 16]

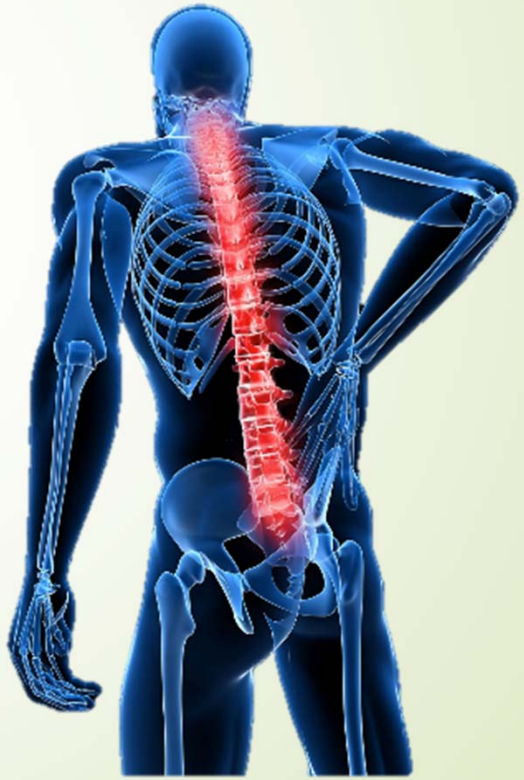
- ALS is a neurodegenerative disease that affects the nerve cells in the brain and the spinal cord
- Medical marijuana helps to manage symptoms of ALS by causing the following:
  - Pain relief
  - Muscle relaxation
  - Dilation of the lungs
  - Improved sleep
  - Appetite stimulation
  - Antioxidative and neuroprotective effects to help prolong neuronal cell survival

Crohn's Disease[18]

- Medical marijuana is useful in Crohn's disease for:
  - Easing pain
  - Limiting frequency of diarrhea
  - Helped with weight gain
- Result of a study concluded that more studies need to be conducted with a larger population to further test the result of marijuana as a pharmacotherapy for Crohn's disease

Severe and Chronic Pain[26]

- Medical marijuana is primarily good at relieving pain
- Components of pain that may respond to cannabis:
  - Neuropathic – burning, piercing
  - Mechanical – dull, aching
  - Inflammatory – acute, sharp
- Can also help with:
  - Spasticity
  - Appetite
  - Mood enhancement

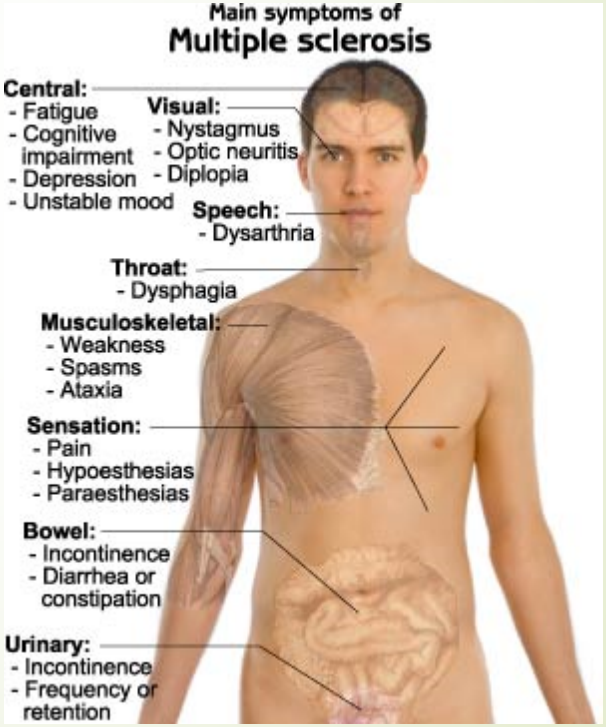


Chronic Pain Conditions[26]

- Some chronic pain conditions that marijuana may help regulate:
  - Myosfacial pain syndrome (MPS)
  - Diabetic neuropathy (DN)
  - Neuropathic pain syndrome (NPS)
  - Central pain syndrome (CPS)
  - Spinal cord injury
  - Fibromyalgia
  - Osteoarthritis (OA)
  - Rheumatoid Arthritis (RA)
  - HIV Neuropathy

Multiple Sclerosis (MS)[27]

- Use of medical marijuana in MS patients helps to relieve severe and persistent muscle spasms/contractions
- Also may provide neuroprotective and anti-inflammatory effects in MS patients
- Neuroinflammation reduced by cannabinoids through regulation of cytokine levels in microglial cells
- Short-term therapy has been seen to be effective, but further studies need to be conducted to assess long-term treatment

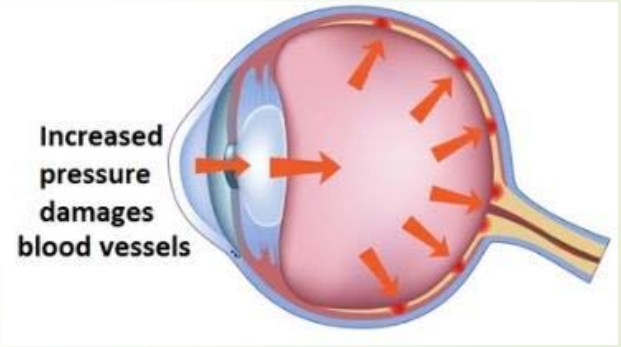


Anxiety

- Natural endocannabinoid system regulates anxiety
  - Lessens excitatory signals that involve the glutamate neurotransmitter
- Chronic and acute stress results in the reduction of endocannabinoids and the responsiveness of the receptors
  - Treatment of medical marijuana helps to increase these levels to relieve the anxiety due to stress

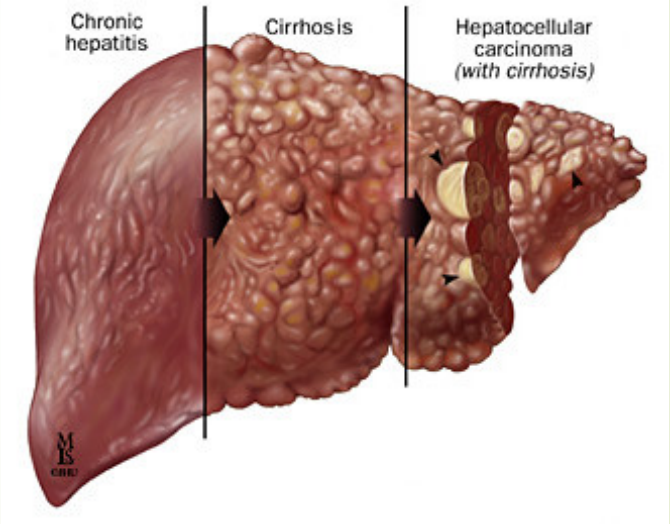
Glaucoma[19]

- A topical formulation would be the ideal form of application
  - Difficult because eye drop form only results in <5% of penetration of the drug according to a study
  - Delivery of medication needs to be refined
- Medical marijuana has neuroprotective properties and can reduce intraocular pressure in those with glaucoma



Hepatitis C[20]

- Medical marijuana used for Hepatitis C patients to for the following:
  - Nausea
  - Moderation of chronic liver disease
  - Reducing inflammation



Adverse events of medical marijuana

Adverse Events Associated with marijuana use[17]

- Chronically smoking marijuana use may cause the following adverse events:
  - Dependence
  - Withdrawal
    - Irritability, depression, insomnia, nausea, obstructive pulmonary disease (COPD), and lung cancer
- Using a vaporizer opposed to smoking may diminish the level of the more toxic components in marijuana
  - Smoking marijuana contains 4 times more tar and 50% more carcinogens than that of tobacco

Detrimental effects of smoking[34,35]

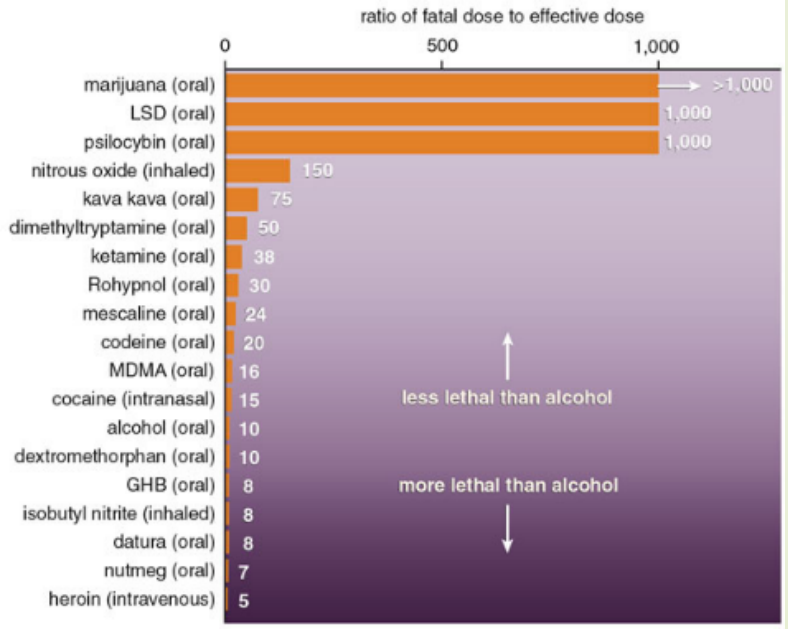
- Can lead to respiratory illness
  - One marijuana cigarette causes as many pulmonary problems as 4-10 tobacco cigarettes
  - Increase risk for bronchitis, emphysema, lung cancer
- Can cause cardiovascular complications
  - Raises blood pressure and heart rate 20-100%
  - 4.8 times risk of hear attack in hour after use

Effects in pregnancy[36]

- Increasing evidence that prenatal exposure can lead to:
  - Increased risk of motor, social, and cognitive disturbances
  - Higher rate of low birth weight in infants and childhood leukemia
- Marijuana has been found in breast milk
  - Avoid when breastfeeding

Acute Toxicities[33]

- Medical marijuana is less lethal than alcohol and many illicit drugs



Toxicology of cannabis

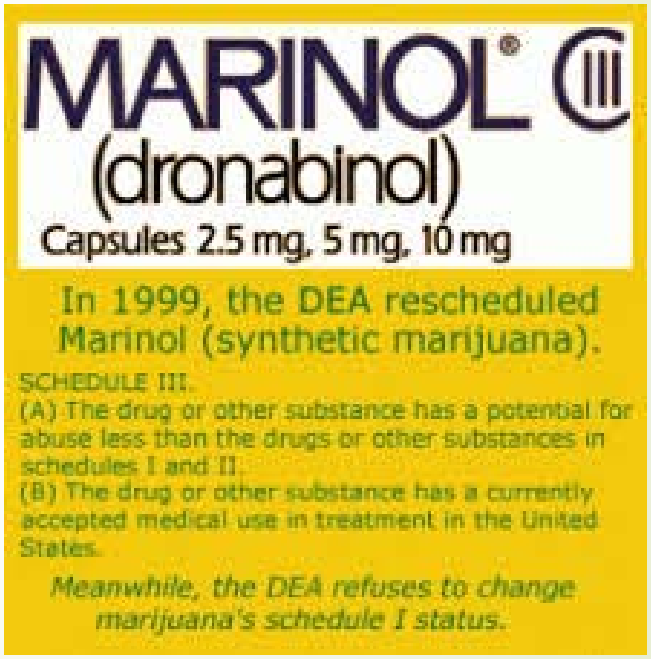
- Has wide therapeutic index
- No known direct deaths
  - Implied association with deaths due to underlying health conditions especially arrhythmias/heart attacks
- Fatal dose is unknown, but implied from animal studies that may be 4000 to 40000 times the highest recreational dose

Pharmaceutical Drugs

Clinical uses

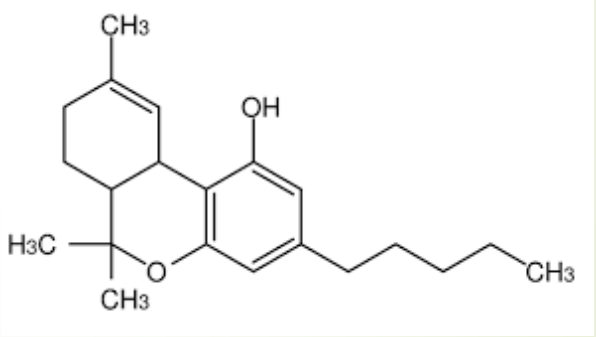
Dronabinol

- Also known as marinol
- FDA-approved
- Produced by Unimed Pharmaceuticals
- It is synthetic THC
- Used for treatment of nausea and vomiting in cancer patients
- Also used as an appetite stimulant and as an analgesic to ease neuropathic pain is MS patients



Dronabinol

- Can be purchased in states that do not have medical marijuana laws
- Bioavailability: 10-20% of IV
  - High first pass metabolism
- Half-life: 60 hours
- Side effects: sedation, mood altered (laughing, elation), confusion



Nabilone

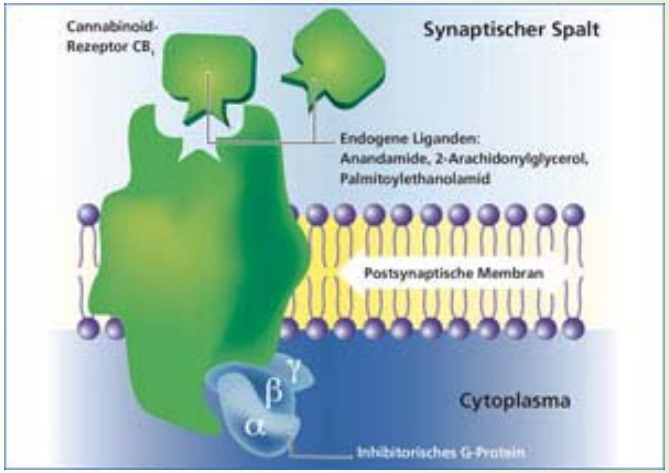
- Also known as Cesamet
- Produced by Valeant Pharmaceuticals International
- Its suggested use is for nausea and vomiting in patients undergoing cancer treatment

Sativex

- Sativex is produced by GW Pharmaceuticals
  - Generic is Nabiximols
  - Approved in UK in June of 2010, not approved in the US
  - Not available in US
- This is a combination of THC and cannabidiol

Sativex

- Formulations: mouth spray or cigarettes
- Uses:
  - Neuropathic pain in patients with Multiple Sclerosis (MS)
  - Adjunct analgesic therapy for cancer patients who have moderate to severe pain and who have already reached the maximum dose of opioid therapy



Rimonabant[37]

- Brand names:
  - Accomplia®
  - Zimulti®
- Not available in the US
- It is a cannabinoid receptor-1 blocker
- Used for the treatment of obesity and nicotine dependence

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The Role of Ketamine in Psychiatry, Addiction, and Pain Management

Background

- Ketamine first synthesized in 1960s as alternative to phencyclinde
- Initially, used as a dissociative anesthetic
- Limited use in contemporary anesthesia due to side effects, namely psychedelic symptoms (Niesters et al. 2013)
- More commonly used in animal anesthesia (Morgan, Curran 2012)
- At subanesthetic doses, produces analgesia

Pharmacology

- A non-competitive antagonist of the NMDA receptor – blocks glutamate action
- S(+) isomer has higher affinity for NMDA receptor than R(-) isomer (Morgan, Curran 2012)
- Also interacts with monoaminergic, muscarinic, and opioidergic receptors (Niesters et al. 2013)

Psychiatric effects

- Emergence symptoms after IV infusion – hallucinations, delusions, 'out-of-body' experiences
- Induces transient symptoms of schizophrenia in healthy patients but no evidence linking chronic ketamine use to diagnosis of psychiatric disorders
- Frequent users exhibited profound impairment of long and short term memory (Morgan, Curran 2012)

Reward and Dependence

- Increases dopaminergic modulation in the brain (similar to other addictive substances) → activates reward pathway
- Interaction with μ opioid receptors may contribute to its rewarding properties
- Some case reports of ketamine dependence but no large scale studies undertaken so incidence of ketamine dependence is unknown
- Frequent users report increasing dose over time (tolerance) (Morgan, Curran 2012)

Role in Alcohol Dependence

- Study by Krupitsky and Grinenko 1997 demonstrated benefit of adding ketamine psychedelic therapy (KPT) to standard therapy
- 65.8% of KPT group showed total abstinence > 1 year compared to 24% of standard treatment group

Role in Depression

- IV infusion of ketamine resulted in rapid antidepressant effect, but only lasted 1-2 weeks
  - 0.5 mg/kg dosing was used in one study
  - Response rates 24 h after ketamine infusion (71%) matched the rates after 6-8 weeks (65%) of standard monoaminergic therapy (Naughton et al. 2014)
- Rapid reduction in suicidal ideation independent of antidepressant effect (Caddy et al. 2014)

Role in Depression

- Dissociative and psychotomimetic effects followed ketamine infusion but did not last longer than 80 min (Caddy et al. 2014)
- Bottom line: ketamine's antidepressant effects peak at 24 h post infusion and generally last 1-2 weeks

Role in Depression

- Clinical use?
- Can provide immediate relief until monoaminergic therapy takes effect
  - Prevent loss of work or school days
  - Reduce suicide
  - Shorten hospital stays
- Overall, good safety profile associated with single dose of ketamine (not enough info on repeated infusions) (Naughton et al. 2014)

Role in Pain Management

- Antagonism of NMDA receptor thought to modulate pain
- Potent analgesic at sub-anesthetic doses (0.5-1 mg/kg/hr) that prevents sensitization of spinal neurons to painful stimuli (Morgan, Curran et al. 2012)
- Roles in acute, chronic, and cancer/palliative care pain

Role in Pain Management

- Acute pain
  - Recommended to start 0.1 mg/kg i.v. ketamine and titrating up with a limit of 0.5 mg/kg
  - Dose required for treating acute pain can lead to loss of consciousness in patients (Persson 2013)
- Chronic Pain
  - A 2003 review of chronic neuropathic pain conditions concluded that evidence for the efficacy of ketamine is moderate to weak
  - Long-term efficacy and safety of ketamine is not well-studied (Persson 2013)

Role in Pain Management

- Not well-established in cancer/palliative care pain (Persson 2013)
  - May be used as adjuvant therapy if standard therapy is not effecive
  - Caution since ketamine may upregulate mTor, which accelerates tumor growth (Naughton et al. 2014)
- Complex Regional Pain Syndrome (CRPS)
  - Current level of evidence is 2B – weak recommendation, moderate quality evidence
  - Need large, well-designed controlled trials (Azari et al. 2012)

Role in Pain Management

- Ketamine in postoperative pain systematic review by Laskowski et al. 2012
  - Treatment group: ketamine + opioid if necessary
  - Placebo group: just opioid
- IV ketamine effective at reducing opioid consumption and delaying time to first analgesic dose in patients with postoperative pain
- Increased neuropsychiatric effects associated with ketamine but reduced postoperative nausea/vomiting (PONV) (Laskowski et al. 2011)

Role in Pain Management

- Postoperative pain (cont.)
- IV ketamine better in some situations
  - Least opioid reduction in head and neck surgery
  - Upper thoracic and abdominal surgeries had greater opioid reduction
  - VAS pain scores > 7/10 showed greatest reduction in opioid use
  - Site of surgery and intensity of pain affect the degree of opioid reduction
- Despite using more opioid, 78% of placebo groups experienced significantly more pain than ketamine treatment groups
  - Implies that ketamine improves overall quality of pain control (Laskowski et al. 2011)

Summary/Conclusion

- Ketamine is still undergoing experimental study in regards to its antidepressant effects, not ready for consistent clinical use
- Ketamine has analgesic properties but has limited use in treating various types of pain
- Well-designed, randomized clinical trials required to corroborate case reports of efficacy
- Further investigation into ketamine's mechanisms of action may elucidate how to better utilize ketamine

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