Pain and Inflammation: Innovations

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5 – Loxin (Boswellia Serratia Extract)\textsuperscript{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
  - Immunosuppressants
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\textsuperscript{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

- **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\textsuperscript{9-11}

- **Side Effects**
  - Diarrhea
  - Gas
  - Bloating

- **Drug interactions**
  - None known
UC-II<sup>12-15</sup>

- 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\textsuperscript{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\textsuperscript{55}
  - 5-HTP was found to have a magnitude of effect similar to SSRIs
  - A number of cases of fatal eosinophilia 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

- 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\textsuperscript{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

- 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

- **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\textsuperscript{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\textsuperscript{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

- 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-κB 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 degradation 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.
- Inhibits 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
- Outsell 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, or 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
References


References


References


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?  

- “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 medications that contain cannabinoids
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.
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 as that with a lower dose and higher quantity.
What are cannabinoids?  

- 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

- Receptors are CB₁ and CB₂
  - CB₁ - mostly expressed in the brain, but also found in adipose tissue, liver, muscle, GI tract, and in reproductive and cardiovascular tissues
  - CB₂ – mostly expressed in immune cells
  - G-protein coupled receptors
CB₁ Receptor

- Effects of CB₁ are neuromodulatory
- Affect the following neurotransmitters:
  - Acetylcholine, norepinephrine, dopamine, serotonin, aminobutyric acid, glutamate, and D-aspartate
CB₂ Receptor

- 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?\textsuperscript{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?\textsuperscript{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

- 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\textsuperscript{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\textsubscript{1/2} distribution: 0.5hr
- T\textsubscript{1/2} elimination: 30hr
- Smoking THC mimics IV
Pharmacokinetics of oral THC

- 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

- 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\textsuperscript{32}

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

\begin{itemize}
\item Pharmacodynamics, PD
\item Drug Action and Mechanism
\item Absorption, Distribution, Metabolism, Excretion
\item Pharmacokinetics, PK
\end{itemize}
PK/PD Model of THC_{32}^{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

- 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

- 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

- 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

- 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

- 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

- 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)\textsuperscript{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

- 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

- 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
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)  

- 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
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

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\textsuperscript{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\textsuperscript{34,35}

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

- 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

- 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 in 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\textsuperscript{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
6. Center for Medicinal Cannabis Research, “Report to the Legislature and Governor of the State of California presenting findings pursuant to S8847 which created the CMCR and provided state funding,” University of California, (San Diego, CA: February 2010), p. 10.


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

- Ketamine first synthesized in 1960s as alternative to phencyclidine
- 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
- $S(+) \text{ isomer has higher affinity for NMDA receptor than } R(-) \text{ isomer}$  
  (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 effective
  - 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
References


