Introduction

- Marijuana, or Cannabis, has quickly become one of the fastest growing industries in the U.S.
- Legal sales from just two states, Colorado (1.5 billion) and Washington (1 billion), exceeded $2 billion in 2017 alone. Nearly 10 billion dollars in USA
- Will no doubt see increase use, however, controversy remains in legalizing cannabis for medical purposes due to the fact that its therapeutic properties are still generally unknown.

Introduction

- Cannabis sativa has its roots in Asia, where its earliest known medical use was from Chinese Emperor Shen Nung in 2727 B.C.
- In 1961, the discovery of the endocannabinoid system in humans, involving receptors for cannabis, paved the way for further research for the use of Marijuana.
Marijuana products are predominantly comprised of two varieties of the cannabis plant:
- **Sativa**
- **Indica**

- **Sativa** produces an uplifting and energetic effect
- **Indica** produces a relaxing and calming effect

**Pharmacology**
- As many as 400 active compounds and 104 cannabinoids
- **Primary active cannabinoids**
  - Delta-9-tetrahydrocannabinol (THC) - psychoactive
  - Cannabidiol (CBD) - non-psychoactive
- Cannabinoids exert their effects on two known G-protein receptors in the body, CB1 & CB2
  - CB1 receptors are found primarily in the central and peripheral nerve terminals and modulate neurotransmitter release
  - CB2 receptors are found mainly on immune cells, where they mediate cytokine release

**Pharmacology**
- Endocannabinoids and their receptors are found throughout body: brain, organs, connective tissues, glands, and immune cells
- In each tissue, the cannabinoid system performs different tasks; goal is always homeostasis
- The anatomical location of cannabinoid receptors:
  - CB1 receptors: nervous system, connective tissues, gonads, glands, organs
  - CB2 receptors: immune system and associated structures
- Endocannabinoids are substances our bodies make naturally to stimulate CB1 and CB2
  - Anandamide
  - 2-arachidonoylglycerol (2-AG)
Pharmacology

<table>
<thead>
<tr>
<th>Structure</th>
<th>Anandamide regulates</th>
<th>Resultant Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>Inhibit GLU &amp; info transfer between body &amp; brain</td>
<td>Decreased pain sensitivity</td>
</tr>
<tr>
<td>Autonomic Nervous System</td>
<td>Inhibit AcH release, HR regulation, urination regulation</td>
<td>HR stimulation, sometimes urination</td>
</tr>
<tr>
<td>Parasympathetic System</td>
<td>Inhibit GLU release, HR regulation, blood vessel constriction</td>
<td>Delayed reduction in HR and blood pressure</td>
</tr>
<tr>
<td>Neuronal Cells</td>
<td>Inhibit GLU-induced excitotoxicity</td>
<td>Neuroprotective effect – prevent cell injury</td>
</tr>
<tr>
<td>Adipose Tissue</td>
<td>Stimulate lipogenesis</td>
<td>Increased adiposity, insulin resistance</td>
</tr>
<tr>
<td>Reproductive tissue</td>
<td>Reduce testosterone, luteinizing hormone</td>
<td>Reduced fertility, altered menstrual cycle</td>
</tr>
<tr>
<td>Skin</td>
<td>Reduce histamine</td>
<td>Anti-inflammatory effect</td>
</tr>
<tr>
<td>General</td>
<td>Reduce in inactivity, eating, sleeping, targeting</td>
<td>Provided relief from stress, reduction of injury</td>
</tr>
<tr>
<td>General</td>
<td>Inhibit immune &amp; lymphocytes, natural killer cells</td>
<td>Anti-inflammatory activity</td>
</tr>
</tbody>
</table>

The action of THC on the CB1 receptors in the CNS causes euphoria but can also induce psychosis.

Cannabidiol is not psychoactive, and has a lower affinity for cannabinoid receptors.

It is thought to exert anti-inflammatory, antianxiety, antipsychotic effects, and possibly have neuroprotective effects.

Therefore, the relative amounts of these two compounds in a given formulation of medical marijuana can greatly impact the therapeutic effects.

This ratio can vary significantly between the multiple available products and formulations.

CB1 receptors in the body are primarily responsible for many of the clinical effects of marijuana.

Most notably pain modulation.
Pharmacology

- Marijuana acts on CB1 receptors, both centrally and peripherally.
- The majority of the CB2 receptors are found on immune cells such as monocytes, neutrophils, mast cells, “B” and “T” cells, and natural killer cells.
- Contributes to the process of inflammation, and thus various pain pathways, including neuropathic pain.

- Because CB2 receptors are absent from brain tissue, modulating pain via this mechanism presents an attractive alternative to mechanisms using CB1 receptors.
- CB1 – focused mechanisms are limited due to unwanted CNS side effects.

Pharmacology

- Cannabinoids have several effects on the gastrointestinal system.
  - Antiemetic properties
  - Appetite – stimulating properties
  - Reducing symptoms of GI conditions such as:
    - Inflammatory bowel disease
    - Crohn’s disease
Medical Cannabis Formulations

- Buds of plants
- Wax dabs - extremely potent (95% THC)
- Vape pen to heat & activate marijuana without toxins
- Tincture for under tongue and mouth
- Cookies, gummies, chips, chocolate bars
- Topicals: creams, body butters, lip balms, patches
- Typical joint

Medical Cannabis Formulations

The most common route of medical marijuana is via inhalation, either directly smoked or through a device.

Active marijuana compounds may be taken orally, ingested as food or drink, or administered topically, via oromucosal spray.

Medical Cannabis Formulations

Common Routes of Administration

- Lungs: vaporized or smoked organic material, hash, hash oil
  - Onset: seconds to minutes
  - Duration: 1-3 hours
- Gut: oral ingestion of lipophilic, alcoholic, supercritical fluidic extract of plant
  - Onset: 0.5 to over 2 hours
  - Duration: 4-8 hours
Medical Cannabis Formulations

- Skin: topical application of creams, tinctures, and patches made from plant extracts
  - Onset: 15-40 minutes
  - Duration: 0.75 – 2 hours

Medical Cannabis Formulations

- It is important to realize that lack of federal approval and regulation may lead to products with varying degrees of purity, strength, cannabinoid (THC: cannabidiol) ratio, and labeling differences
  - It is vital that users and prescribers be aware of these facts when choosing or recommending any product from a dispensary

Single Molecule Pharmaceuticals

- Two synthetic cannabinoid compounds have been approved by the FDA
  - Dronabinol (Marinol)
  - Nabilone (Cesamet)
  - Available in pill form
  - Treatment of chemotherapy – induced nausea and vomiting, as well as appetite stimulation associated with AIDS (dronabinol only)
Single Molecule Pharmaceuticals
- Sativex (nabiximols) is an oromucosal spray available in Canada and the United Kingdom but still pending approval in the U.S.
- Epidiolex (cannabidiol) is still under investigation in the U.S. for childhood seizures

Medical Cannabis Use
- Over 90% of use is for severe pain
- About 25 to 30% is used for muscle spasms and M.S.
- Approximately 13% is used for nausea
- About 5% of individuals use cannabis for cancer
- Other uses: seizures and epilepsy, glaucoma, and HIV/AIDS

Medical Cannabis Use
- Patients and caregivers often look for treatments other than the conventional therapies to alleviate symptoms for a variety of medical conditions
- The government has a limited number of growers for marijuana research, and access for research is limited
- To date, the FDA has not approved marijuana as a safe and effective drug for any indication
The FDA has approved the use of the synthetic compounds Marinol and Cesamet, however, they have not approved any drug product containing or derived directly from Marijuana.

The FDA is aware that there is considerable interest in the use of THC to treat a number of medical conditions that include: glaucoma, AIDS, wasting syndrome, neuropathic pain, MS, seizure disorders, and chemotherapy – induced nausea.

The use and/or study of marijuana for numerous medical conditions has been steadily growing as more states legalize its use for both medicinal and recreational purposes.

THC is viewed as a potential alternative to traditional FDA-approved therapies for many conditions (Table 1).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Marinol (dronabinol)</th>
<th>Cesamet (nabilone)</th>
<th>Cannabinoid &amp; THC combination</th>
<th>Cannabinoids / Cannabis sativa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite stimulation</td>
<td></td>
<td></td>
<td></td>
<td>More trials are needed to determine if benefits exist</td>
</tr>
<tr>
<td>AIDS</td>
<td></td>
<td></td>
<td></td>
<td>More trials are needed to determine if benefits exist</td>
</tr>
<tr>
<td>Cancer Pain</td>
<td></td>
<td></td>
<td>X</td>
<td>Evidence supports a benefit</td>
</tr>
<tr>
<td>Chemotherapy-induced nausea &amp; vomiting</td>
<td>X</td>
<td></td>
<td></td>
<td>Evidence supports a benefit</td>
</tr>
<tr>
<td>Childhood seizures</td>
<td></td>
<td>X</td>
<td></td>
<td>More trials are needed to determine if benefits exist</td>
</tr>
<tr>
<td>Glaucoma</td>
<td></td>
<td></td>
<td></td>
<td>Evidence supports a benefit</td>
</tr>
<tr>
<td>Multiple sclerosis bladder frequency</td>
<td></td>
<td></td>
<td></td>
<td>Evidence supports a benefit</td>
</tr>
<tr>
<td>Multiple sclerosis neuropathic pain</td>
<td>X</td>
<td></td>
<td></td>
<td>Evidence supports a benefit</td>
</tr>
<tr>
<td>Multiple sclerosis peripheral pain</td>
<td></td>
<td></td>
<td></td>
<td>Evidence supports a benefit</td>
</tr>
<tr>
<td>Multiple sclerosis central pain or facial spasm</td>
<td></td>
<td></td>
<td></td>
<td>Evidence supports a benefit</td>
</tr>
<tr>
<td>Multiple sclerosis spasticity</td>
<td></td>
<td></td>
<td></td>
<td>Evidence supports a benefit</td>
</tr>
<tr>
<td>Neurologic injury</td>
<td></td>
<td></td>
<td></td>
<td>More trials are needed to determine if benefits exist</td>
</tr>
</tbody>
</table>
National Academies: Health Effects of Cannabis

**Conclusive or substantial evidence** that cannabis or cannabinoids are *effective*:
- for treatment of chronic pain in adults (cannabis)
- for improving patient-reported multiple sclerosis (MS) spasticity symptoms, but limited evidence for clinician-measured spasticity (oral cannabinoids)
- As anti-emetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids)

---

National Academies: Health Effects of Cannabis

**Moderate evidence** that cannabinoids, primarily nabiximols, are *effective*:
- To improve short-term sleep outcomes in patients with sleep disturbance associated with obstructive sleep apnea, fibromyalgia, chronic pain, and MS

---

National Academies: Health Effects of Cannabis

**Limited evidence** that cannabis or oral cannabinoids are *effective for*:
- increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids)
- improving symptoms of Tourette syndrome (THC capsules)
- improving anxiety symptoms in individuals with social anxiety (cannabinoids)
- improving symptoms of posttraumatic stress disorder (nabiximols)
- better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage - statistical association

**Limited evidence** that cannabis or oral cannabinoids are *ineffective for*:
- improving symptoms of dementia (cannabinoids)
- improving intraocular pressure associated with glaucoma (cannabinoids)
- reducing depressive symptoms in individuals with chronic pain or MS (nabiximols, dronabinol, and nabilone)
National Academies: Health Effects of Cannabis

- No or insufficient evidence to support or refute that cannabinoids are effective for:
  - Cancer-associated anorexia, cachexia syndrome, and anorexia nervosa
  - Cancers, including gliona
  - Irritable bowel syndrome
  - Epilepsy
  - Myoclonus in patients with paralysis due to spinal cord injury
  - Chorea and certain neuropsychiatric symptoms associated with Huntington’s disease
  - Symptoms associated with amyotrophic lateral sclerosis (ALS)
  - Parkinson’s disease or levodopa-induced dyskinesia
  - Dystonia
  - Treatment for mental health outcomes in individuals with schizophrenia or schizophreniform psychosis
  - Achieving abstinence in the use of addictive substances

Adverse Effects

- Adverse effects may occur with both short-term and long-term use
  - Acute effects of marijuana have been shown to include alterations in short-term memory, coordination and judgment
  - Elderly patients may suffer from current medical conditions such as dementia, vision/hearing changes, and mobility issues that may already impact their ability to perform these tasks

Adverse Effects

- Tachycardia
- Palpitations
- Hypertension
- Coughing
- Wheezing
- Sputum production
- Lethargy, Sedation, Slowed Reaction-Time
- Psychological dysfunction: impaired coordination, memory formation, recollection, focus
- Visual Disturbances

EUPHORIA

Nervous System
Adverse Effects

- Dronabinol (Marinol) and Nabilone (Casamet) CNS related effects: dizziness, vertigo, drowsiness, ataxia, and euphoria
- Cannabinoid hyperemesis, is rare, but can be severe for the elderly patient
  - This syndrome characterized by cyclic episodes of uncontrolled nausea and vomiting that lasts several days and often does not respond to antiemetic therapy

Adverse Effects

- Long term, consistent use, of marijuana can present additional undesirable side effects such as worsening anxiety, depression, and other psychoses
- Physical problems from long-term marijuana use in the elderly may be associated with negative respiratory effects, including increased risk of upper respiratory infections, pneumonia, and chronic bronchitis

Adverse Effects

- Long-term use of marijuana may impact cardiovascular health and increase the risk of myocardial infarction, stroke, and peripheral vascular disease as suggested by research
- These adverse effects are especially relevant to the elderly that are already at greater risk of suffering from psychiatric, pulmonary, and cardiovascular problems
- Additionally, abrupt cessation of long-term regular marijuana use may produce withdrawal symptoms: anxiety, insomnia, irritability, dysphoria, and craving
Toxicity

- Acute toxicity and overdose are possible with the consumption of medical marijuana
- Large single doses of marijuana may precipitate acute psychoses; CNS depression which can lead to respiratory depression has been reported; cardiovascular and neurologic toxicity have also been reported

Toxicity

- There are pharmacokinetic differences between smoking and oral ingestion of THC
- Smoking marijuana has rarely been reported to cause acute toxicity because of the predictability of rapid time-to-peak; this allows for ease of self-titration
- Oral formulations however, generally reach peak concentrations within one to two hours, but this may be delayed up to six hours after ingestion
- Users have been known to redose before drug effects have been fully realized, increasing the potential for accidental overdose

Special Considerations in the Elderly

In the elderly, susceptible to additive CNS effects, cannabis for medical treatment must be screened for clinically important drug to drug interactions

- Chlorpromazine
- Clobazam
- Clozapine
- CNS depressants
- Divalprox
- Hexobarbital
- Hydrocortisone
- Ketoconazole
- Protease inhibitors (indinavir, nelfinavir)
- MAO inhibitors
- Phenytoin
- Theophylline
- Tricyclic antidepressants
- Warfarin

*Note: significant synergistic interaction found between CBD and levitiracetam. Significant antagonistic interactions noted with THC and clozapine and CBD = cannabidiol. (AES Annual Meeting December 2015)
### Special Considerations in the Elderly

<table>
<thead>
<tr>
<th>Concomitant Drug/Drug Class</th>
<th>Description of Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Marijuana smoking increased clearance of chlorpromazine</td>
</tr>
<tr>
<td>Clobazam</td>
<td>Increased clobazam levels (60-80% higher) with CBD use</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Possible increased clonazepam metabolism by marijuana induction of CYP1A2</td>
</tr>
<tr>
<td>CNS Depressants (e.g., alcohol, benzos)</td>
<td>Additive drowsiness and CNS depression</td>
</tr>
<tr>
<td>Dilazepam</td>
<td>Possible hypomanic / psychotic reaction</td>
</tr>
<tr>
<td>Hexobarbital</td>
<td>Enhance CNS depressant effect. CBD decreased metabolism but did not have effect</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>THC increased serum cortisol, but effect blunted in frequent users</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Peak THC concentration increased by 27%</td>
</tr>
<tr>
<td>MAO inhibitors</td>
<td>Possible enhancement of orthostatic hypotension</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>May enhance CNS depressant effect. Possible increased phenytoin metabolism by marijuana induction</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Significant decrease in peak concentration of indinavir and nelfinavir</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Smoked marijuana lowers theophylline concentrations</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>May cause transient cognitive changes, delirium, or tachycardia</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Possible enhanced anticoagulant effect</td>
</tr>
</tbody>
</table>

Its is imperative to explain the risks of marijuana therapy to elderly patients, including an assessment of the potential for abuse and misuse, similar to opioid prescribing stewardship.

- A thorough patient and family history can be used to assist in identifying addiction potential.
- Validated tools to assist are available and include the “Screening, Brief Intervention and Referral for Treatment” or the “Cannabis Use Disorder test.”
The American Pharmacist Association recommends marijuana products be screened on the patients’ medication profiles in a fashion similar to the way of tobacco, alcohol, and other substances. Therapeutic effects of marijuana largely depend on THC concentration in a given formulation and dosage form, therefore, it is essential to consider method of dose delivery, such as inhalation versus oral. This lack of standardization and variety of marijuana strains make it difficult to predict the common side effects and drug to drug interactions of marijuana.

Smoking marijuana seems to have more predictable and therapeutic peak plasma concentration compared with oral formulations. This is a very important consideration when using these products for the elderly.

With the lack of large scale trials in the elderly it is imperative to dose, using the golden rule, “start low and go slow.” There is a lack of standard dosing recommendations, for marijuana across all dosage forms. Most studies to date refer to kinetics of marijuana in the normal, average, healthy adult. Special considerations with regard to altered pharmacokinetics in the elderly must be taken into consideration.
In states where marijuana is legal and where multiple dosage formulations are available...

- It is essential to educate residents on the proper use of such products
- What steps to take if too much marijuana is consumed
- The importance of purchasing marijuana from a reputable dispensary to ensure purity

It is also imperative to educate the resident’s family and caregiver on the risks and benefits of marijuana use as well as the adverse effects

- How to monitor for signs and symptoms of overdose (acute psychosis, shortness of breath, pupil dilation, or a fast heart rate)
- In working with providers, it is up to the pharmacist to communicate relevant drug to drug and drug to disease interactions

Pharmacists must work together with other medical providers to educate elderly residents on marijuana use with a similar plan of care to avoid potential confusion

- It is critical that health care providers work together to thoroughly evaluate the resident’s medical diagnoses and concurrent medication to ensure patient safety
Medical Cannabis & Opioid Use

Limited evidence that there is less opioid overdose deaths than expected in states with legal medical marijuana.

John Avolio, Clinical Pharmacist, BCGP

States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%, P = .003) compared with states without medical cannabis laws.

This association strengthened over time:
- Year 1: −19.9%; 95% CI, −30.6% to −7.7%; P = .002
- Year 2: −25.2%; 95% CI, −40.6% to −5.9%; P = .01
- Year 3: −23.6%; 95% CI, −41.1% to −1.0%; P = .04
- Year 4: −20.2%; 95% CI, −33.6% to −4.8%; P = .02
- Year 5: −33.7%; 95% CI, −50.9% to −10.4%; P = .006
- Year 6: −33.3%; 95% CI, −44.7% to −19.6%; P < .001

Medical Marijuana: Ohio's Law

- In the U.S. State of Ohio, cannabis is illegal for recreational use, but possession up to 100 grams is decriminalized.
- Legislation to allow a regulated system of medical marijuana cultivation, sale, and possession in 2016, but the system did not come into effect until 2017.
Decriminalization

- On August 22, 1975, the governor signed a bill decriminalizing cannabis
- Ohio became the sixth state to do so
- Under Ohio law, the possession of up to 100 grams is a "minor misdemeanor" which carries a maximum fine of $150
- Possession of more than 100 grams but less than 200 grams of marijuana is a misdemeanor punishable by up to thirty days in jail and a $250 fine

Partial Legalization of Medical Cannabis

- In June 2016, Governor John Kasich signed House Bill 523, which permits the medical use of marijuana in some cases
- The bill, sponsored by state representative Stephen Huffman, was approved by an 18-15 vote in the state senate and by a 67-29 vote in the State House

Partial Legalization of Medical Cannabis

- The bill sets up a rule making process under which a "state-run or licensed system of growing facilities, testing labs, physician certification, patient registration, processors, and retail dispensaries" will be established
- The statute "requires the system to be fully operational by September 2018", with the Ohio Department of Commerce to make rules for cultivators by May 6, 2017, to issue rules and regulations for cultivators, and the remainder of rules to be promulgated by October 2017
Once the law is fully effective, eligible patients will be able to obtain medical marijuana at state-licensed dispensaries.

In September 2018, the program will be fully operational.

Several forms of medical marijuana are legal in Ohio:
- Inhalation of marijuana through a vaporizer (not direct smoking)
- Oils
- Tinctures
- Plant material
- Edibles
- Patches
- Any other forms approved by the State Board of Pharmacy

Qualifying medical conditions for medical marijuana are specified in the law as:
- HIV/AIDS
- Amyotrophic lateral sclerosis (Lou Gehrig’s disease)
- Alzheimer’s disease
- Cancer
- Chronic traumatic encephalopathy
- Cystic fibrosis
- Epilepsy or other seizure disorder
- Fibromyalgia
- Glaucoma
- Hepatitis C
- Inflammatory bowel disease
- Multiple sclerosis (MS)
- Pain: either chronic, severe, or intractable (difficult to manage)
- Parkinson’s disease
- Post-traumatic stress disorder (PTSD)
- Sickle cell anemia
- Spinal cord disease or injury
- Tourette’s syndrome
- Traumatic brain injury
- Ulcerative colitis
Medical Marijuana Highlights (Ohio Law)

- In order for a patient to be eligible to obtain medical marijuana, a physician must make the diagnosis of one of the qualifying conditions.
- Medical marijuana is not appropriate for all patients with these conditions.
- Recreational use of marijuana is still illegal in Ohio.

Medical Marijuana Highlights (Ohio Law)

- Patients wanting to use medical marijuana must apply to the State Board of Pharmacy for a registration card.
- The application must be submitted on their behalf by a physician approved by the Ohio State Medical Board who possesses a certificate to recommend medical marijuana.

Medical Marijuana Highlights (Ohio Law)

- Only those physicians who obtain this certificate will be eligible to recommend medical marijuana.
- The application must show that the patient has been diagnosed with a qualifying medical condition, and that a physician-patient relationship exists.
**Medical Marijuana Highlights (Ohio Law)**

- There are significant long- and short-term risks of marijuana use, including with medical marijuana. A physician should be consulted to understand both the risks and the possible benefits of medical marijuana for the patient.
- Even if medical marijuana was recommended by a doctor, the new Ohio law does not prevent employers from taking action if an employee violates the company’s drug policy against marijuana use.

**Conclusion**

- Current status of cannabis is Schedule I, yet allowed in most states.
- Cannabis and its active components impact the endocannabinoid system to provide various effects.
- Many dosage formulations of cannabis available to patients.
- Clinical studies performed in children and adults demonstrate some effectiveness for certain conditions; adverse effects are reported in all studies so benefits and risks must be carefully weighed.
- Potential drug interactions and patient safety concerns are important issues for pharmacists to address with patients using cannabis.
- Pharmacists have an important role in monitoring and education related to cannabis use.