Medical Marijuana
What is it? What is its efficacy?
And what are the risks?

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DISCLOSURE
We work hard so our dogs can have a better life.
Case Presentation

• 29 year old woman admitted to resident service 3/19/19
• CC: Abdominal pain, N&V
• HPI: Multiple admissions for abdominal pain, Relief with hot shower
• PMH: 10 years s/p heart transplant
• Social hx: Smokes marijuana daily to self-medicate for anxiety
Clinical Questions

• What are the potential drug interactions – patient is on immunosuppressive regimen?
• What are the risks of smoking marijuana daily?
• Should we worry about withdrawal from marijuana?
• Is marijuana useful to treat anxiety?
• What is Cannabis Hyperemesis Syndrome?
Why Healthcare Professionals Need to Know About Medical Marijuana

• Whether recommending medical marijuana or not, healthcare professionals need to be knowledgeable about it.
• Patients will ask healthcare professionals for their medical opinion.
• Patients may be using medical marijuana or recreational marijuana from another source.
Challenges for Professionalism

• The FDA process provides important safeguards for patients and physicians. Medical marijuana is neither an FDA-approved drug nor a dietary supplement.

• Education in medical schools and residencies is lacking.

• There are concerns about quality control, dosage formulations.

• Evidence of efficacy, side effects, and drug interactions is inadequate.

• Dispensed in dispensaries rather than pharmacies.

• Medical marijuana may be diverted for recreational use.

• 10% or more users may become addicted.
“Legalization” of medical marijuana (MM) has changed the paradigm of medical practice

• “Recommended” rather than prescribed
• Illegal under federal law - DEA Schedule 1 drug – “No currently accepted medical use in treatment in the US.”
• Use directed by legislature rather than scientific bodies
  • Approved qualifying conditions
  • Variety of delivery systems
• Little or no evidence of efficacy for most conditions
• Limited data on side effects and drug interactions
• Promoted both by cannabis industry and media
• No reproducible dosing
Composition of Marijuana

• The *Cannabis sativa L* plant contains over 400 substances and over 60 cannabinoids.

• The main psychoactive constituent of *Cannabis sativa L* is delta-9-tetrahydrocannabinol (THC).

• Cannabidiol (CBD) is a THC antagonist with antipsychotic, immunomodulating, and anti-inflammatory effects.

• Because increased cannabidiol leads to decreased available THC, some growers breed CBD out.
Drug-Drug Interactions

- Opioids
- Barbiturates
- CNS depressants
- Protease inhibitors
- SSRIs
- Sildenafil
- Theophylline
- Tricyclic antidepressants
- Anticholinergics
- Sympathomimetics
- Alpha agonists
- Naltrexone
- Disulfiram
- Lithium
- Neuroleptic antipsychotics
- Anesthetic agents

Am J Health-Sys Pharm, May 2007
Marijuana-Drug Interactions: THC

- THC-metabolized by CYP2C9 and CYP 3A4
- Poor metabolizers of CYP2C9 – have THC levels 3 X higher than extensive metabolizers
- Inhibitors of CYP2C9 increase plasma levels of THC (drugs like amiodarone, cimetidine, cotrimazole, metronidazole, fluvoxamine, fluconazole, etc)

- Ketoconazole (inhibitor of CYP3A4) increases peak conc and AUC of THC 1.2-1.8 fold, with greater increases in the conc of THC metabolites
- CYP3A4 inhibitors, clarithromycin, erythromycin, cyclosporine, verapamil, itraconazole, boceprevir, are likely to increase THC conc.
- Rifampin (CYP3A4 inducer) - reduces THC levels some 20-40%
Marijuana-Drug Interactions: Cannabidiol (CBD)

- CBD is substrate of CYP3A4 and CYP2C19 – ketoconazole, an inhibitor CYP3A4, increases plasma CBD levels by about 2 X
- Rifampin, an inducer of CYP 3A4, decreases CBD levels by 50-60%
- Other inhibitors and inducers should do the same
- Omeprazole, a modest inhibitor of CYP2C19, did not alter the plasma levels of CBD in one study
Adverse Effects

Adverse effects include:

• Tachycardia
• Hypotension
• Conjunctival injection
• Bronchodilation
• Muscle relaxation
• Decreased gastrointestinal motility

Because cannabinoid receptors, unlike opioid receptors, are not located in the brainstem areas controlling respiration, LETHAL overdoses from marijuana and cannabinoids do not occur. A smoker would have to consume nearly 1,500 pounds of marijuana within about fifteen minutes to induce a lethal response.
Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

<table>
<thead>
<tr>
<th>Table 1. Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects of short-term use</strong></td>
</tr>
<tr>
<td>Impaired short-term memory, making it difficult to learn and to retain information</td>
</tr>
<tr>
<td>Impaired motor coordination, interfering with driving skills and increasing the risk of injuries</td>
</tr>
<tr>
<td>Altered judgment, increasing the risk of sexual behaviors that facilitate the transmission of sexually transmitted diseases</td>
</tr>
<tr>
<td>In high doses, paranoia and psychosis</td>
</tr>
<tr>
<td><strong>Effects of long-term or heavy use</strong></td>
</tr>
<tr>
<td>Addiction (in about 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users)*</td>
</tr>
<tr>
<td>Altered brain development*</td>
</tr>
<tr>
<td>Poor educational outcome, with increased likelihood of dropping out of school*</td>
</tr>
<tr>
<td>Cognitive impairment, with lower IQ among those who were frequent users during adolescence*</td>
</tr>
<tr>
<td>Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general population)*</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
</tr>
<tr>
<td>Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders</td>
</tr>
</tbody>
</table>

* The effect is strongly associated with initial marijuana use early in adolescence.
Psychiatric Illness can be worsened with cannabis use

• Psychosis and schizophrenia
  • Paranoia, hallucinations more likely to reoccur if experienced with early use
  • Increased risk of schizophrenia in adolescents
  • Increased risk for those with first degree relative with psychotic disorder
  • Daily marijuana use (2.6X risk), high drug potency (1.6X risk), and exposure younger than age 15 (1.6X risk) increase risk of psychotic disorder

• Depression

• Anxiety
  • May lower anxiety in some individuals, but at higher doses, appears to cause anxiety in most individuals

• Post Traumatic Stress Disorder (PTSD)

Lancet Psychiatry 2019 Published Online March 19, 2019 http://dx.doi.org/10.1016/S2215-0366(19)30048-3
Cannabis Withdrawal

A. Cessation of cannabis use that has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months).

B. Three (or more) of the following signs and symptoms develop within approximately 1 week after cessation:
   1. Irritability, anger, or aggression.
   2. Nervousness or anxiety.
   3. Sleep difficulty (e.g., insomnia, disturbing dreams).
   4. Decreased appetite or weight loss.
   5. Restlessness.
   6. Depressed mood.
   7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache.
Medical Marijuana: Ohio’s Law

• As of September 8, 2016, it is legal for Ohio residents with certain medical conditions to use non-smoking forms of medical marijuana when recommended by an eligible physician.

• Eligible patients will be able to obtain medical marijuana at state-licensed dispensaries, staffed by non-medical personnel.

• In 2019, the program will be fully operational.
How will a patient get medical marijuana?

- Schedule appointment;
- Be evaluated by physician with certificate to recommend;
- Be diagnosed (or have prior diagnosis confirmed) with qualifying medical condition;
- Have physician give recommendation and register patient; and
- Purchase product at dispensary
Medical Board Expectations for Physicians Recommending Marijuana

• Patient-Physician Relationship
• Patient Evaluation
• Informed and Shared Decision Making
• Consultation and Referral
• Medical Records

• Treatment Agreement
• Qualifying Conditions
• Ongoing Monitoring
• Physician Conflicts of Interest
• Physician Use of Marijuana
What are the Qualifying Conditions?

- AIDS
- Amyotrophic lateral sclerosis
- Alzheimer’s disease
- Cancer
- Chronic traumatic encephalopathy
- Crohn’s disease
- Epilepsy or another seizure disorder
- Fibromyalgia
- Glaucoma
- Hepatitis C
- Inflammatory bowel disease

- Multiple sclerosis
- Pain that is either chronic and severe or intractable
- Parkinson’s disease
- Positive status for HIV
- Post-traumatic stress disorder
- Sickle cell anemia
- Spinal cord disease or injury
- Tourette’s syndrome
- Traumatic brain injury
- Ulcerative colitis
What are the Permissible Forms of Medical Marijuana?

- 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
# Marijuana Products in Ohio

<table>
<thead>
<tr>
<th>Type of Marijuana Product</th>
<th>THC content (%) allowable</th>
<th>90-day supply equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier I plant material</td>
<td>Up to 23%</td>
<td>8 ounces</td>
</tr>
<tr>
<td>Tier II plant material</td>
<td>23.1-35%</td>
<td>5.3 ounces</td>
</tr>
</tbody>
</table>
| Extracts used for other forms, not plant material | Up to 70%                 | - 9.9 grams of an edible form  
- 26.55 grams in lotion, patches, creams,  
& other topical forms  
- 53.1 g. in oil for vaporization |

Reference
What else do I need to know about Ohio’s medical marijuana law?

- The law prohibits smoking medical marijuana or growing it at home.
- Recreational use of marijuana is still illegal in Ohio.
- 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.
  - The application must show that the patient has been diagnosed with a qualifying medical condition, and that a physician-patient relationship exists.
- 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.
Challenges for Health Professionals: Medical Marijuana

Marijuana is not a homogeneous material; the term “medical marijuana” therefore does not refer to a single, consistent substance or entity.

The composition of medical marijuana, including its THC content, varies widely depending on the strain, cultivation, storage, and harvesting practices, etc.

The methods of medical marijuana administration—smoked/vaporized, baked goods, teas, infused honeys, elixirs, candies, etc.—do not ensure patient dosing is identifiable, standardized, and reproducible.
Systematic Reviews


• Guidance for the use of medicinal cannabis in Australia—Overview. Dec 2017. ~120 pages

• Simplified Guideline for Prescribing of Medical Cannabinoids in Primary Care. Canadian Fam Phys Feb 2018. 9 pages
Simplified guideline for prescribing medical cannabinoids in primary care

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Abstract

Objective To develop a clinical practice guideline for a simplified approach to medical cannabinoid use in primary care, the focus was on primary care application, with a strong emphasis on best available evidence and a promotion of shared, informed decision making.

Methods The Evidence Review Group performed a detailed systematic review of 4 clinical areas with the best evidence around cannabinoid pain, nausea and vomiting, spasticity, and adverse events. Nine health professionals (2 generalist family physicians, 2 pain management-focused family physicians, 1 inner-city family physician, 1 neurologist, 1 oncologist, 1 nurse practitioner, and 1 pharmacist) and a patient representative comprised the Prescribing Guideline Committee (PGC), along with 2 nonvoting members (pharmacist project managers). Member selection was based on profession, practice setting, location, and lack of financial conflicts of interest. The guideline process was iterative through content distribution, evidence review, and telephoned and online meetings. The PGC directed the Evidence Review Group to address and provide evidence for additional questions as needed. The key recommendations were derived through consensus of the PGC. The guideline was drafted, refined, and distributed to a group of clinicians and patients for feedback, then refined again and finalized by the PGC.

Recommendations Recommendations Include limiting medical cannabinoid use in general, but also outline potential restricted use in a small subset of medical conditions for which there is some evidence (neuropathic pain, palliative and end-of-life pain, chemotherapy-induced nausea and vomiting, and spasticity due to multiple sclerosis or spinal cord injury). Other important considerations regarding prescribing are reviewed in detail, and content is offered to support shared, informed decision making.

Conclusion This simplified medical cannabinoid prescribing guideline provides practical recommendations for the use of medical cannabinoids in primary care. All recommendations are intended to assist with, not dictate, decision making in conjunction with patients.

Editor’s key points

• This simplified prescribing guideline was developed with a primary care focus. Guideline contributors were selected based on profession, practice setting, and location to represent a variety of key stakeholders (particularly primary care) from across the country, as well as on the absence of financial conflicts of interest.
• Although cannabinoids have been promoted for an array of medical conditions, the evidence base is challenged by bias and a lack of high-level research. Two large evidence synopses suggested that only 2 conditions have an adequate volume of evidence to inform prescribing recommendations: chronic pain, nausea and vomiting, and spasticity.
• The guideline suggests that clinicians should consider medical cannabinoids for refractory neuropathic pain and refractory pain in palliative care, chemotherapy-induced nausea and vomiting, and spasticity in multiple sclerosis and spinal cord injury after reasonable trials of standard therapies have failed. If considering medical cannabinoids and criteria are met, the guideline recommends nabiximor or nabiximol to be tried first. Prices are generally more common than benefits are, and it is important to discuss the benefits and risks of medical cannabinoids with patients for whom they are being considered.
Box 1. Recommendations summary

General recommendation
• We recommend against use of medical cannabinoids for most medical conditions owing to lack of evidence of benefit and known harms (strong recommendation)
  - Potential exceptions are reviewed below: some types of pain, CINV, and spasticity due to MS or SCI
Summary of Systematic Reviews

All three systematic reviews concluded:

- There are 3 conditions where medical marijuana has modest efficacy
  - Neuropathic pain
  - Chemotherapy induced nausea and vomiting
  - Subjective spasticity in MS
- Medical marijuana is not a first-line treatment for any condition.
63 y.o. male, long time runner, fell off ladder 7 months ago, unable to drive easily, needs cane.

Post-spinal surgery after laminectomy—herniated disc L2

Previously on gabapentin and tramadol/acetaminophen.

Has now had three surgeries for never-ending pain and now has recurrent numbness, severe pain on standing and weakness below knees.
Chronic Non-Cancer Pain

• There is some evidence that medical marijuana can reduce pain in both MS-related neuropathic pain and non-MS-related neuropathic pain, but for many people the reduction in pain may be modest.

• There is insufficient information to make a conclusion about medical marijuana for the treatment of pain associated with arthritis and fibromyalgia
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pooled odds ratio (95% CI)</th>
<th>Pooled event rate (%), cannabinoid vs placebo</th>
<th>Number needed to treat to benefit (NNTB) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30% reduction in pain</td>
<td>1.46 (1.16-1.84)</td>
<td>29.0% vs 25.9%</td>
<td>24 (15-61)</td>
</tr>
<tr>
<td>50% reduction in pain</td>
<td>1.43 (0.97-2.11)</td>
<td>18.2% vs 14.4%</td>
<td>*</td>
</tr>
<tr>
<td>Patient global impression of change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived “much” to “very much” improved</td>
<td>1.62 (1.34-1.96)</td>
<td>18.9% vs 11.8%</td>
<td>38 (27-62)</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause adverse events</td>
<td>2.33 (1.88-2.89)</td>
<td>81.2% vs 66.2%</td>
<td>6 (5-8)</td>
</tr>
<tr>
<td>Study withdrawals—adverse events</td>
<td>3.47 (2.64-4.56)</td>
<td>15.8% vs 4.6%</td>
<td>40 (35-49)</td>
</tr>
</tbody>
</table>

Bold font indicates a statistically significant result. Only categorical outcomes with a moderate or higher GRADE rating are reported here.

* Number needed to treat to benefit unable to be calculated as the pooled odds ratio crossed the line of no effect.

CI, confidence interval.
Figure 2. Neuropathic pain: Pharmacotherapy treatment.

**Outcome:** Meaningful (approximately 30%) pain improvement
Ordered by decreasing estimated efficacy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Outcome Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>25 Improve with treatment, 25 improve with placebo or no treatment, 50 no improvement</td>
</tr>
<tr>
<td>High-dose opioids*</td>
<td>18 improve with treatment, 25 improve with placebo or no treatment, 57 no improvement</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>17 improve with treatment, 25 improve with placebo or no treatment, 58 no improvement</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>16 improve with treatment, 25 improve with placebo or no treatment, 59 no improvement</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>15 improve with treatment, 25 improve with placebo or no treatment, 60 no improvement</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>13 improve with treatment, 25 improve with placebo or no treatment, 62 no improvement</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>9 improve with treatment, 25 improve with placebo or no treatment, 66 no improvement</td>
</tr>
</tbody>
</table>

**Limitations**
- Based on indirect comparisons
- Time frame approximately 4-12 wk
- Details on methods available from CFPlus*

*60-110 mg of oral morphine per day.
*Go to the full text of the article online and click on the CFPlus tab.
Medical marijuana and multiple sclerosis

• Nabiximols, which are an extract of cannabis plant containing roughly equal amounts of THC and CBD are approved in Australia for use in MS for muscle spasticity.

• 5 of 10 studies carried out on other cannabinoids concluded that there was evidence that medical marijuana may be effective for symptoms of pain and/or spasticity and positive effects on sleep and bladder symptoms.

• 5 other studies were inconclusive or did not show that treatment with medical marijuana had any positive effect in MS.
Preventing and managing chemotherapy induced nausea and vomiting in cancer (CINV)

• There are some reports that medicinal cannabis products (in particular THC and related substances) relieved the symptoms of CINV.

• While several studies found that the medicinal cannabis products were as effective as the prescription medicine it was compared with, most of the research studies were carried out some years ago, and in recent years much more effective prescription medicines for nausea and vomiting have become available.

• THC-rich medicinal cannabis products for CINV should be prescribed only after standard approved treatments have failed.
Dronabinol

• In 1986, an isomer of synthetic delta-9-THC in sesame oil was licensed and approved by the FDA for the treatment of chemotherapy-associated nausea and vomiting under the name dronabinol.

• Clinical trials determined that dronabinol was as effective as or better than other antiemetic agents available at the time.

• Dronabinol was also studied for its ability to stimulate weight gain in patients with AIDS in the late 1980s. Thus, the indications were expanded to include treatment of anorexia associated with HIV infection in 1992. Clinical trial results showed no statistically significant weight gain, although patients reported an improvement in appetite.
Medical marijuana use in palliative care

• Little evidence of any benefit to advanced cancer patients with chronic pain.
• Little effect on appetite, nausea/vomiting, pain, dizziness, mental health or sleep problems.
• No evidence that medicinal cannabis has any anti-cancer activity in human studies or that it can slow the progression of these conditions.
• In people without AIDS, there is also no evidence that medical marijuana will increase their appetite, that it will help the patient gain weight or that it will enhance their mood.
FDA News Release

FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy

For Immediate Release

June 25, 2018

The U.S. Food and Drug Administration today approved Epidiolex (cannabidiol) [CBD] oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older. This is the first FDA-approved drug that contains a purified drug substance derived from marijuana. It is also the first FDA approval of a drug for the treatment of patients with Dravet syndrome.

CBD is a chemical component of the Cannabis sativa plant, more commonly known as marijuana. However, CBD does not cause intoxication or euphoria (the “high”) that comes from tetrahydrocannabinol (THC).

It is THC (and not CBD) that is the primary psychoactive component of marijuana.

“This approval serves as a reminder that advancing sound development programs that properly evaluate active ingredients contained in marijuana can lead to important medical therapies. And, the FDA is committed to this kind of careful scientific research and drug development,” said FDA Commissioner Scott Gottlieb, M.D. “Controlled clinical trials testing the safety and efficacy of a drug, along with careful review through the FDA’s drug approval process, is the most appropriate way to bring marijuana-derived treatments to patients. Because of the adequate and well-controlled clinical studies that supported this approval, prescribers can have confidence in the drug’s uniform strength and consistent delivery that support appropriate dosing needed for treating patients with these complex and serious epilepsy syndromes. We’ll continue to support rigorous scientific research on the potential medical uses of marijuana-derived products and work with product developers who are interested in bringing patients safe and effective, high quality products. But, at the same time, we are prepared to take action when we see the illegal marketing of CBD-containing products with serious, unproven medical claims. Marketing unapproved products, with uncertain dosages and formulations can keep patients from accessing appropriate, recognized therapies to treat serious and even fatal diseases.”
Medical marijuana is not appropriate for:

- Age <25
- Personal or family history of psychotic disorders
- Personal history of cannabis use disorder or active substance abuse disorder
- People with significant cardiovascular or respiratory disease
- Women who are pregnant, planning to become pregnant or breastfeeding
- Patients with neurological conditions may be more likely to experience negative effects from medical marijuana


Guidance for the use of medicinal cannabis in Australia, Patient Information, Version1, December 2017
General cautions

• Doctors should:
  • carefully assess elderly and particularly sensitive patients
  • regularly monitor interactions between medical marijuana and other treatments.
  • assess liver function when deciding to continue or stop treatment.

• Although there may be some evidence to suggest a benefit from medical marijuana treatment for one condition or symptom, this does not mean it will have benefits for other conditions, even with the same product and the same dose.

• There is very limited evidence to show how medical marijuana reacts with medications.

Guidance for the use of medicinal cannabis in Australia, Patient Information, Version1, December 2017
Key References


• Kleber HB and DuPont RL, Physicians and Medical Marijuana: Am J Psychiatry 169:6, June 2012


• Guidance for the use of medicinal cannabis in Australia—Overview
Where Can I Go For Additional Information?

• Ohio Medical Marijuana Control Program  
  www.medicalmarijuana.ohio.gov

• Ohio State Medical Board  
  http://med.ohio.gov/Apply/Certificate-to-Recommend-CTR

• U.S. Drug Enforcement Administration  
  www.dea.gov

• Ohio State Medical Association  
  www.osma.org