

Medical Marijuana – A Brief Overview of the Program in Ohio and Pharmacology of Cannabinoids

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Objectives

- **Describe a broad overview of the Medical Marijuana Control Program in Ohio**
- **Discuss the pharmacology of cannabinoids**

Background

- **Federal Controlled Substance Act:**
 - “Marihuana” means all parts of a plant of the genus *cannabis*, whether growing or not; the seed of a plant of that type; the resin extracted from a part of a plant of that type; and every compound, manufacture, salt, derivative, mixture, or preparation of a plant of that type or of its seeds or resin.

Ohio Medical Marijuana Control Program. <http://medicalmarijuana.ohio.gov/>

Who is Responsible?

Department of Commerce

- Cultivators
- Processors
- Testing laboratories

State Board of Pharmacy

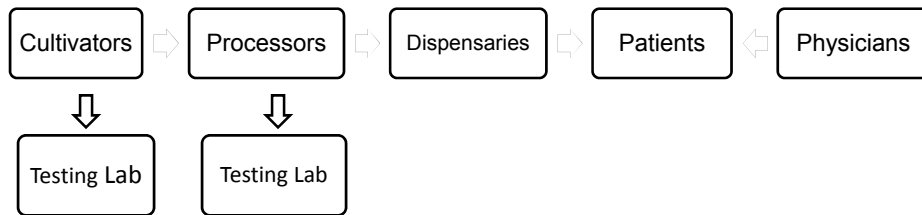
- Dispensaries
- Patients/Caregivers
- New forms and methods of medical marijuana

Medical Board

- Certified physicians
- New qualifying conditions

<http://medicalmarijuana.ohio.gov/>

Medical Marijuana Process Flow Chart



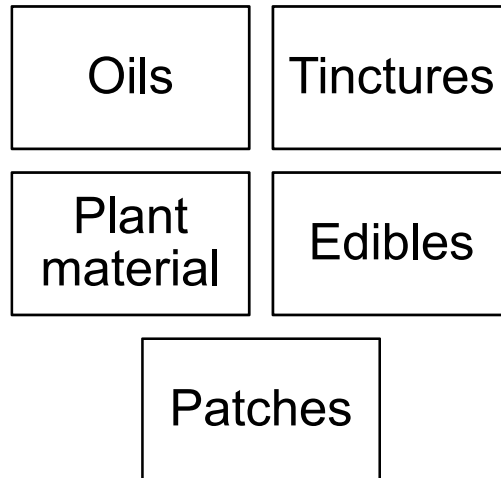
<http://medicalmarijuana.ohio.gov/>

Dispensaries

- **Must have proof of registration and recommendation prior to dispensing**
- **Must submit data to Ohio Automated Rx Reporting System (OARRS)**
- **No healthcare professional required to dispense**
 - **Policy must exist for education of patients**
 - **Employee must have documented training**
 - **Must maintain 16 CE hours/2 year licensing period**

<http://medicalmarijuana.ohio.gov/>

House Bill 523-Approved Forms



<http://medicalmarijuana.ohio.gov/>

Certificate to Recommend (CTR) Eligibility

- **Active, unrestricted license**
- **OARRS registration**
- **DEA registration**
- **No prior action on license from DEA or any licensing entity for inappropriate prescribing**
- **2 hours of approved CME**
- **No defined conflict of interest**
 - **Ownership/investment in or compensation agreement with a medical marijuana entity/applicant**

Proposed rules: Physician rules document. Ohio Medical Marijuana Control Program Web site.

Qualifying Medical Conditions

Infection - HIV/AIDS, Hep C

Inflammatory Bowel Disease - Crohn's, Ulcerative Colitis

Neurologic Conditions - Seizure/Epilepsy, Tourette's

Neurodegenerative - Alzheimer's, ALS, MS, Parkinson's

**CNS Trauma - Traumatic Brain Injury/Encephalopathy, Spinal
Cord Injury**

Psychiatric - PTSD

Chronic Pain, Fibromyalgia, Sickle Cell Anemia

Other - Glaucoma, Cancer

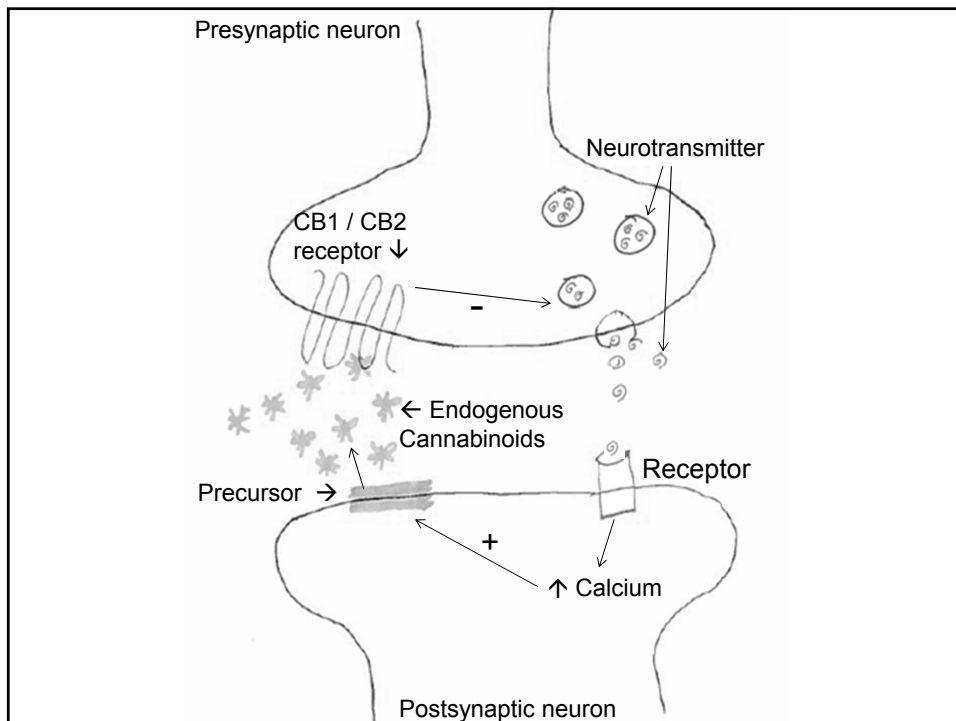
Ohio Medical Marijuana Control Program. <http://medicalmarijuana.ohio.gov/>

Pharmacology of Cannabinoids

Types of Cannabinoids

- Endocannabinoids
- Phytocannabinoids
 - Δ -9 tetrahydrocannabinol (THC)
 - Cannabidiol (CBD)
 - Cannabinol (CBN)
- Synthetic
 - Pharmaceutical
 - Illicit

JAMA. 2015 Jun 23-30;313(24):2474-83
Dialogues in Clinical Neuroscience. 2017;19(3):309-316.



Importance of Constituents

- **THC trends over time**
 - 1980s ~4%
 - 2012 average concentration from police confiscation ~15%
 - 2015 ~20% with potencies up to 30%
- **Percentage of constituents and ratios play a role in therapeutic applications, adverse effects, etc.**
- **Entourage effect**

1) "Marijuana far more potent than it used to be, tests find" article. CBS News Web site. Published 3/23/2015. 2) Trends Pharmacol Sci. 2009 Oct;30(10):515-27.

Primary Clinical Implications of THC and CBD

- **THC**
 - **Psychoactive**
 - emotional and cognitive changes, analgesia, hypothermia and appetite stimulation
- **CBD**
 - **Non-psychotropic**
 - Modulation of behavioral effects

Recent patents on CNS drug discovery. 2012;7(1):25-40

Pharmacokinetics

PK Parameter	Smoked/Vaporized	Oral Ingestion
Onset	Seconds – minutes	30 – 120 minutes
Peak	6 – 10 minutes	4 – 6 hours
Distribution	Highly lipophilic, accumulates in fatty tissues and reaches peak concentrations in 4-5 days. Tissue $t_{1/2}$ = ~7 days with complete elimination taking up to 30 days	
Metabolism	Phase 1 & 2 in liver	
11-OH-THC metabolite (active)	Lower concentrations	Higher concentrations
Elimination $t_{1/2}$ (chronic use)	THC = 4.1 days 11-OH-THC = 12.6 days	

Adapted from Chemistry & biodiversity. 2007;4(8):1770-1804

Drug/Drug Interactions

- **Metabolism**
 - **THC and CBN**
 - **CYP 3A4 & 2C9**
 - **CBD**
 - **CYP 3A4 & 2C19**
- **Synergy with CNS depressants**
- **Opioids: Cross tolerance and mutual potentiation**

Res Social Adm Pharm. 2015 Sep 16. pii: S1551-7411(15)00170-9

Cannabinoids Used With Opioids

Observational Findings of Interest

- **Medicare opioid prescriptions**
- **Self-reported reduction in opioid use**
- **Synergy for analgesia**
- **Cannabinoids demonstrate analgesia sans opioids**

1) Health Aff. 2017;36:945–51. 15. 2) J Pain. 2016;17:739–44. 3) Drug Alcohol Depend. 2015;147:144–50. 4) J Pain Symptom Manag. 2003;25:496–98. 5) J Pain Symptom Manag. 2010;39:167–79. 6) J Pain. 2008;9:254–64. 7) J Pain. 2012;13:438–49 8) Neuropsychopharmacology. 2018 Sep;43(10):2046-2055.

Substance Abuse Considerations

- **Rx opioids + cannabis =**
 - **↑ Cannabis Use Disorder?**
 - **Problematic Opioid Use Behaviors?**
 - **↓ tolerance and dependence?**
 - **↓ discriminative stimulus and reinforcing effects of opioids?**

1) Am J Addict. 2015;24:538–45. 2) Drug Alcohol Depend. 2015;147:144–50.

Bachhuber et al, 2014

- **States with medical cannabis laws had 24.8% lower mean annual opioid overdose mortality rate**
- **Lower rates of overdose mortality strengthened over time**

JAMA Intern Med. 2014;174(10):1668-1673.

Summary

- **Medical Marijuana dispenses on OARRS**
- **Be aware of drug – drug interactions**
- **Constituents matter**
- **Cannabis + opioids**

Medical Marijuana

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Problem

- Internet search almost any disease along with the word “marijuana” and you will find support for using marijuana to treat the disease.
- 29 U.S. States, Washington D.C., Puerto Rico and Guam have “legalized” marijuana, including Michigan, Pennsylvania and Ohio.
 - 9 States for recreational use in adults
- What do medical providers need to know?

Take Home Points

- 1) Medical marijuana is ancient and many people feel that marijuana is benign.
- 2) There is evidence supporting use of medical marijuana in a few specific clinical conditions.
- 3) However, clinical research of marijuana is extremely limited.
- 4) There are known dangers of marijuana, and, as clinicians it is our duty to educate patients about these dangers.

Outline

- **Background**
 - **Biology**
 - **History**
- **Attitudes**
- **Therapeutics**
- **Dangers**

Biology - Plant

- **Cannabis**
 - ~500 chemical compounds – e.g. terpenes, flavonoids have been isolated from the Cannabis plant.
 - >100 different cannabinoids
 - Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive cannabinoid.
 - Cannabidiol (CBD) is the cannabinoid in Epidiolex.
 - Hemp and Marijuana are both cannabis and they can cross fertilize.
 - Hemp has no more than trace THC.
 - Marijuana has significant amounts of THC concentrated in the flower-female buds.
 - Cannabis can occur as separate male and female plants and as a plant with both male and female parts.

Biology - Animal

- **Two identified receptors**
 - **CB1, CB2**
 - **On separate genes on different chromosomes**
 - **G-proteins**
 - **Inhibitory effect on neurotransmitter release and uptake**
 - **CB1**
 - **Central Nervous System - primarily**
 - **Lower concentration throughout the body**
 - **CB2**
 - **Microglia**
 - **Macrophages**
 - **Spleen**

History to 1900

- **~5000 years ago – Medicinal use of marijuana is described in Chinese and Indian texts**
- **~2000 year ago – The psychotropic effects of marijuana are described in Chinese medical texts**
- **Middle-ages – Hemp and marijuana are widely disseminated for “industrial” and medical use**
- **1800’s - In the U.S. Cannabis is a more economically important crop than tobacco**
- **1850 – Marijuana is widely use and is added to U.S. Pharmacopeia**

History since 1900 (U.S.)

- **1906 - Pure Food and Drug Act**
- **1914 - Harrison Act - Marijuana is criminalized**
- **1930s - AMA opposes marijuana use**
- **1936 - Refer Madness – movie “trailer”**
- **1937 - Marijuana Tax Act - \$100/ounce, \$1/ounce if for medical use**
- **1970 - Controlled Substance Act – Schedule 1**
- **1980s-'90s - Cannabinoid receptors, endogenous**
- **1996 - 1st Medical Marijuana bill - California**

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Attitudes towards Marijuana

- **On-line survey of 16,280 adults**
- **United States**
- **2017**
- **55% (9003) responded**

Ann Intern Med. 2018;169:282-90. doi:10/7326/M18-0810

Attitudes towards Marijuana

- **Benefits**
 - **81% believe marijuana has at least 1 benefit**
 - **66% Pain Management**
 - **48% Epilepsy, Multiple Sclerosis**
 - **47% Anxiety, Stress, Depression**
 - **29% agree that smoking marijuana prevents health problems**

Ann Intern Med. 2018;169:282-90. doi:10/7326/M18-0810

Attitudes towards Marijuana

– Risks

- **91% believe marijuana has at least 1 risk**
 - **52% Legal**
 - **50% Addiction**
 - **42% Impaired Memory**

Ann Intern Med. 2018;169:282-90. doi:10/7326/M18-0810

Attitudes towards Marijuana

– Beliefs that marijuana is benign

- **18% believe second-hand marijuana smoke is safe for adults**
- **7.6% believe second-hand marijuana smoke is safe for children**
- **7.3% believe marijuana is safe during pregnancy**
- **22% believe marijuana is not addictive**

Ann Intern Med. 2018;169:282-90. doi:10/7326/M18-0810

Attitudes towards Marijuana

- **Beliefs that marijuana is benign**
 - Survey of >20,000 children in grades 6 through 12
 - 9% of middle-school and high-school students in the U.S. report having used electronic cigarettes to vaporize cannabis.
 - 25% reported ever using e-cigarettes
 - 31% of these reported ever vaping cannabis
 - 23% of middle-school e-cigarette users
 - 33% of high-school e-cigarette users

JAMA Pediatr. Published online 9/17/2018. doi:10.1001/jamapediatrics.2018.1920

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Effects of Medical Marijuana

- **Increased**
 - Euphoria
 - Appetite
 - Sedation
 - Psychosis (unmasking?)
- **Decreased**
 - Pain
 - Nausea
 - Spasticity
 - Memory/Cognition
 - Locomotor function

Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders. Report of the Guideline Development Subcommittee of the American Academy of Neurology. Koppel, et al. Neurology 2014. 82:1556-63. doi.org/10.1212/WNL.0000000000000363

The Health Effects of Cannabis and Cannabinoids 2017 National Academies of Sciences, Engineering, and Medicine (NASEM)

- **Conclusive or substantial evidence for improving**
 - Chronic pain in adults
 - Nausea
 - Chemotherapy-induced Nausea/Vomiting
 - Patient-reported spasticity in Multiple Sclerosis
- **Moderate evidence for improving**
 - Short term sleep in sleep apnea, fibromyalgia, multiple sclerosis, and chronic pain

National Academies Press (US); 2017 Jan 12. ISBN-13: 978-0-309-45304-2 ISBN-10: 0-309-45304-6

**The Health Effects of Cannabis and
Cannabinoids 2017
National Academies of Sciences, Engineering,
and Medicine (NASEM)**

- **Limited evidence for improving**
 - Anorexia and weight loss in HIV/AIDS
 - Not as effective as megestrol acetate (Megace)
 - Objective spasticity in Multiple Sclerosis
 - Social Anxiety (public speaking test)
 - Post-Traumatic Stress
 - Tourette syndrome
 - Traumatic Brain Injury or Hemorrhage
- **Limited evidence for NOT improving**
 - Dementia
 - Glaucoma
 - Depression associated with chronic pain or MS

National Academies Press (US); 2017 Jan 12. ISBN-13: 978-0-309-45304-2 ISBN-10: 0-309-45304-6

**The Health Effects of Cannabis and
Cannabinoids 2017
National Academies of Sciences, Engineering,
and Medicine (NASEM)**

- **Insufficient evidence for**
 - Cancer
 - Cancer-associated anorexia-cachexia
 - Irritable Bowel
 - Epilepsy
 - Spasticity not due to Multiple Sclerosis (MS)
 - Amyotrophic Lateral Sclerosis (ALS)
 - Huntington Disease – chorea, neuropsychiatric
 - Parkinson Disease or levodopa dyskinesia
 - Dystonia
 - Drug addiction
 - Schizophreniform psychosis

National Academies Press (US); 2017 Jan 12. ISBN-13: 978-0-309-45304-2 ISBN-10: 0-309-45304-6

Qualifying Medical Conditions in Ohio

- **Infectious**
 - HIV/AIDS, Hepatitis C
 - Possibly for associated anorexia/cachexia, but NOT for the underlying disease.
- **Inflammatory Bowel Disease**
 - Crohn Disease, Ulcerative Colitis
 - Possibly for associated pain or anxiety, but NOT for the underlying disease.
- **Seizure/Epilepsy**
 - Not supported by current evidence.
- **Tourette Syndrome**
 - Supported by limited evidence.

Qualifying Medical Conditions in Ohio (continued)

- **Neurodegenerative**
 - Alzheimer Dementia
 - Evidence against improving or slowing progression.
 - Amyotrophic Lateral Sclerosis (ALS)
 - Not supported by current evidence.
 - Multiple Sclerosis (MS)
 - Reduced spasticity supported by current evidence.
 - Parkinson Disease
 - Not supported by current evidence.

Qualifying Medical Conditions in Ohio (continued)

- **Central Nervous System Trauma**
 - **Traumatic Brain Injury/Encephalopathy,
Spinal Cord Injury**
 - **Supported by limited evidence.**
- **Psychiatric**
 - **Post-Traumatic Stress Disorder (PTSD)**
 - **Supported by limited evidence.**
- **Chronic Pain**
 - **Fibromyalgia, Sickle Cell Anemia**
 - **Supported for treatment of chronic pain.**

Qualifying Medical Conditions in Ohio (continued)

- **Cancer**
 - **Not supported by current evidence.**
- **Chemotherapy-associated
nausea/vomiting**
 - **Supported by current evidence.**
- **Glaucoma**
 - **Evidence against benefit.**

Conditions for which cannabinoids work, and don't

- **Yes, supported by current evidence**
 - **Pain**
 - **Nausea**
 - **Anxiety**
 - **Insomnia**
 - **Spasticity in Multiple Sclerosis**
 - **Seizures in Lennox-Gastaut/Dravet**
- **No, not supported by current evidence**
 - **Dementia**
 - **Depression**
 - **Glaucoma**
 - **Cancer**

FDA-Approved Cannabinoids (Schedule II)

- **Dronabinol (Marinol, Syndros)**
 - **anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS)**
 - **nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments**
- **Nabilone (Cesamet)**
 - **nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments**
- **Cannabidiol (Epidiolex)**
 - **seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older**

Nabiximols

- Trade name - Sativex
- A 1:1 THC:CBC extract of Cannabis
- Oral spray
- approved as a botanical drug in the United Kingdom in 2010 to alleviate neuropathic pain, spasticity, overactive bladder, and other symptoms of multiple sclerosis

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Adverse Effects of Medical Marijuana

- **Central Nervous System**
 - Sedation, dizziness, numbness, cognitive impairment, slowed reaction time, sensory disturbances
 - Dysphoria, anxiety, nightmares, psychosis
- **Cardiovascular**
 - Hypotension, hypertension, tachycardia, palpitations
- **Gastrointestinal**
 - Dry mouth, nausea, hyperemesis
- **Long term**
 - Immunosuppression, decreased fertility

Res Social Adm Pharm. 2015 Sep 16. pii: S1551-7411(15)00170-9.

Acute Toxicity / Overdose

- **Psychosis**
- **CNS Depression**
 - Sedation
 - Confusion
 - Psychomotor retardation
- **Cardiovascular**
 - Hypotension
 - hypertension
 - tachycardia

Consult Pharm. 2017 Jun 1;32(6):341-351

Acute Toxicity / Overdose

- **More common with edible formulations**
 - **Educate, encourage to minimize risk to children**

Consult Pharm. 2017 Jun 1;32(6):341-351

Neurodevelopment

- **Human studies - associations**
 - **Slower cognitive processing**
 - **Poorer learning/memory**
 - **Psychiatric disorders**
- **Animal studies – rats**
 - **Poorer learning/memory**
 - **Abnormal social interactions**
 - **Addictive behavior**

Future Neurol. 2011 Jul 1; 6(4): 459–480

Driving Impairment

- **Independent risk factor for motor vehicle accidents**
- **Associated with increased fatality in motor vehicle accidents**
- **Avoid driving**
 - **Inhalation – 4 hours**
 - **Oral ingestion – 6 hours**
 - **Euphoria experienced – 8 hours**

J Pain Palliat Care Pharmacother. 2009;23(1):4-25. 2) "Authorizing Dried Cannabis for Chronic Pain or Anxiety". The College of Family Physicians of Canada Website.

Cannabis Use Disorder

- **10 – 30 % of users develop**
- **DSM-5 Diagnostic Criteria - at least two in the prior 12 months**
 - **Increasing use over time**
 - **Inability to control consumption**
 - **Use with negative impacts on social, professional or educational life**
 - **Craving**
 - **Withdrawal syndrome, e.g. hyperemesis**

Subst Abuse Rehabil. 2016 May 3;7:41-53

Cannabis Withdrawal Syndrome

- **Symptoms**
 - **Anxiety**
 - **Depression**
 - **Sleep disturbance**
 - **Irritability**
 - **Anorexia and weight loss**

Subst Abuse Rehabil. 2016 May 3;7:41-53

Proposed Contraindications and Cautions

Contraindications

- **Age under 25**
- **Personal or family history of psychosis and/or schizophrenia**
- **Current or past history of cannabis use disorder**
- **Active substance use disorder**
- **Significant cardiovascular or respiratory disease**
- **Pregnancy or breast feeding**

Cautions

- **Concurrent active mood or anxiety disorder**
- **Use of tobacco**
- **Heavy user of alcohol, opioids, and/or benzodiazepines**

Can J Anaesth. 2016 May;63(5):608-624

Take Home Points

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