

## 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



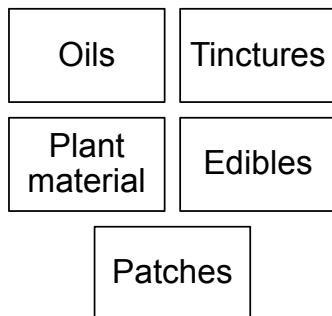
<http://medicalmarijuana.ohio.gov/>

## 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

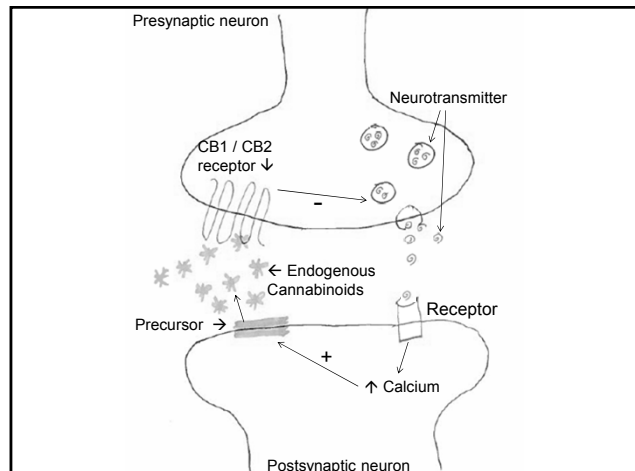
Ohio Medical Marijuana Control Program. <http://medicalmarijuana.ohio.gov/>

## Pharmacology of Cannabinoids

## Types of Cannabinoids

- Endocannabinoids
- Phytocannabinoids
  - $\Delta$ -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-psychoactive
    - 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

**Harrison G. Weed, MS, MD**  
Professor of Internal Medicine  
The Ohio State University College of Medicine Chair,  
Pharmacy & Therapeutics Executive Committee  
The Ohio State University Wexner Medical Center

## 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 - 1<sup>st</sup> Medical Marijuana bill - California

## Outline

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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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