

MEDICAL MARIJUANA: A Pharmacist's Guide

JENNIFER KAPUR, PHARM.D.

PHARMACIST, HARBORVIEW MEDICAL CENTER
 CLINICAL ASSISTANT PROFESSOR, UNIVERSITY OF WASHINGTON SCHOOL OF PHARMACY
 INSTRUCTOR OF NURSING, SEATTLE PACIFIC UNIVERSITY

Disclosures

The speaker has no financial or other conflicts of interest to report

Objectives

- Review federal and state laws regarding the use of marijuana
- Describe the components of marijuana and their pharmacologic effects
- Review the dosage forms of medical marijuana
- Discuss the risks and benefits of medical marijuana use

Learning Self-Assessment Questions

- Where is it legal to write a prescription for medical marijuana?
 - (a) Alaska, Oregon, Washington, California and Colorado
 - (b) Alaska, Oregon, Washington, California, Colorado and Washington DC
 - (c) In all states where medical marijuana has been legalized
 - (d) It is not legal in the US to write a prescription for medical marijuana
- How many phytocannabinoids are found in the cannabis plant?
 - (a) 2-10
 - (b) 20-30
 - (c) 30-50
 - (d) >100

Learning Self-Assessment Questions

- Which cannabis-derived pharmaceutical is not available by prescription in the United States?
 - (a) Dronabinol
 - (b) Nabilone
 - (c) Nabiximols
 - (d) Marinol
- How long after the oral ingestion of medical marijuana is the peak blood concentration of the phytocannabinoid THC seen?
 - (a) 10 minutes
 - (b) 30-60 minutes
 - (c) 2 hours
 - (d) up to 4 hours

Learning Self-Assessment Questions

- A report in JAMA found what percentage of edible marijuana products in three major US cities were labeled accurately?
 - (a) 4%
 - (b) 17%
 - (c) 60%
 - (d) 78%
- The phytocannabinoid THC is metabolized by which cytochrome P450 enzyme(s)?
 - (a) 3A4
 - (b) 3A4 and 2C9
 - (c) 3A4 and 2C19
 - (d) 2C9 and 2C19

History Of Medical Marijuana



William Brooke O'Shaughnessy
Introduced marijuana to Western medicine in the mid-1800s

From
www.en.Wikipedia.org



History Of Medical Marijuana

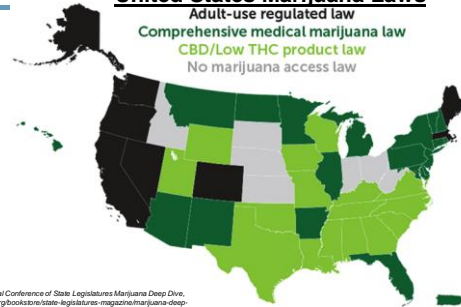
- 1851: Marijuana added to US Pharmacopeia
- 1942: Marijuana removed from US Pharmacopeia
- 1970: Marijuana classified as Schedule 1 under Controlled Substances Act
- 1996: California becomes first state to legalize medical marijuana
- 1998: Alaska, Oregon and Washington legalize medical marijuana
- Currently 28 states and the District of Columbia have legalized medical marijuana

State Marijuana Policies Timeline



The National Conference of State Legislatures Marijuana Deep Dive.
www.ncsl.org/bookstore/state-legislatures-magazine/marijuana-deep-dive.aspx

United States Marijuana Laws

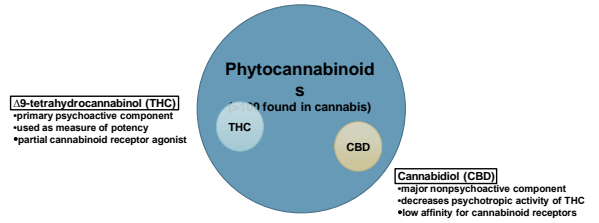


The National Conference of State Legislatures Marijuana Deep Dive.
www.ncsl.org/bookstore/state-legislatures-magazine/marijuana-deep-dive.aspx

Cannabinoids

ENDOCANNABINOIDS	PHYTOCANNABINOIDS (Medical Marijuana)	CANNABIS-DERIVED PHARMACEUTICALS
Endogenous cannabinoids produced in human tissues	Cannabinoids found in the cannabis plant (Cannabis sativa or Cannabis indica)	Prescription drugs containing phytocannabinoids or synthetic cannabinoids
Two identified: •Anandamide •2-arachidonoylglycerol (2-AG)	> 100 compounds identified	Approved by the FDA: •Dronabinol (Marinol®/Syndros®) •Nabilone (Cesamet®) Phase III trials in the US: •Nabiximols (Sativex®) •Cannabidiol (Epidiolex)

Phytocannabinoids



Phytocannabinoids: Potential Targets Of Action In Epilepsy

Phytocannabinoid	Potential Targets of Action in Epilepsy
Δ9-tetrahydrocannabinol (THC)	CB1, CB2, TRPA1, TRPV2, TRPM8, GPR55, 5-HT _{1A} , PPARY, μ- and opioid receptors, PPARY, μ- and opioid receptors, Badrenoreceptors, VGCC, VGKC, VGSC
Δ9-tetrahydrocannabinolic acid (THCA)	TRPA1, TRPV4, TRPM8, DLGα, COX 1, COX 2
Δ9-tetrahydrocannabivarin (THCV)	CB1, CB2, GPR55, TRPA1, TRPV1-4
Cannabidiol (CBD)	TRPV1, VGCC, VGCS, 5-HT _{1A} , 5-HT _{2A} , GPR55, adenosine receptors A1 and A2, VDAC1, TNFα
Cannabivarin (CBDV)	CB1 and CB2 independent—more data needed

<http://dx.doi.org/10.1016/j.ybeh.2016.11.016>

Pharmacologic Actions Of Marijuana

- **CNS**
 - Euphoria, dysphoria, anxiety
 - Heightened sensory perception
 - Generalized CNS depression
 - Mental clouding, memory impairment
 - Incoordination
 - Tolerance
 - Dependence
 - Analgesia
 - Antiemetic, hyperemetic
 - Increased appetite
- **Cardiovascular**
 - Tachycardia
 - Supine hypertension
 - Postural hypotension
- **Other**
 - Decreased intraocular pressure
 - May have antispasmodic effects
 - May have anti-inflammatory effects
 - May have neuroprotective effects
 - Complex immunomodulatory effects

Health Canada: Information for Health Care Professionals—Cannabis and the cannabinoids (2013).

Marijuana Dosage Forms

CANNABIS	HASH	HASH OIL
Flowering tops/leaves/stalks of mature female plant	Dried cannabis resin	Oil based extract of hash
THC content: -historically 0.5-5% -WA recreational MJ: 16% (average)	THC content: -2-20% or higher	THC content: -15-50% or higher

Medical Marijuana Dosage Forms: Administration

INHALATION	ORAL	TRANSDERMAL
Smoking	Capsules	Ointment/Balm
Vaporizers	Oils/Tinctures	Spray
	Edibles:	Suppository
	-Butter/Cooking oils	Patch
	-Soda/Coffee/Wine	
	-Candy/Mints	
	-Baked goods	
	-Crackers	
	-Many others	

Peak Blood [THC] Reached
 INHALED: within 10 minutes
 ORAL: up to 4 hours
 TRANSDERMAL: info not available

Marijuana Dosage Forms: Dose

- Typically a "dose" of recreational marijuana is considered to be 5-10mg THC
- Marijuana from pre-1960s contained more equal proportions of THC and CBD
- Marijuana currently available has been bred to contain higher concentrations of THC

Marijuana Dosage Forms: Accuracy Of Product Labeling For Edibles

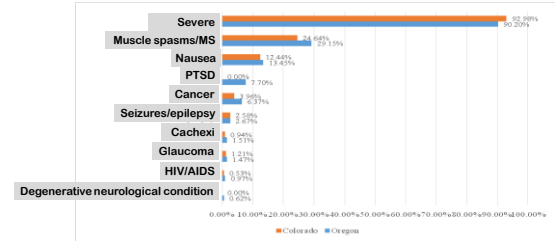
	Accurately Labeled	Underlabeled	Overlabeled
Overall (Seattle, San Francisco, Los Angeles)			
Products tested, N=75	13 (17%)	17 (23%)	45 (60%)
THC (mg) label range	15-200	20-1000	2-325
THC (mg) actual range	15-183	34-1236	<1-267

JAMA. 2015;313(24):2491-2493.

CANNABIS-DERIVED PHARMACEUTICALS in the US

	DESCRIPTION	FORMULATION	INDICATIONS
Synthetic Compounds			
DRONABINOL (Marinol®, C-III) (Syndros®, C-X)	Synthetic THC	Oral capsule (2.5mg, 5mg, 10mg) Oral solution (5mg/mL)	•Chemotherapy-induced NV •HIV associated anorexia w/wt. loss
NABILONE (Cesamet®, C-II)	Synthetic cannabinoid similar to THC	Oral capsule (1mg)	•Chemotherapy-induced NV •HIV associated anorexia w/wt. loss
Natural Product Derived Compounds			
NABIXIMOLS (Sativex®, Phase III)	Cannabis derived extract of THC & CBD	Oral mucosal spray (2.7mg THC and 2.5mg CBD/spray)	•Multiple sclerosis spasticity (approved in 28 countries)
CANNABIDIOL (Epidiolex®, Phase III)	Cannabis derived CBD	Oral solution	Phase III trials in US for: •Dravet syndrome •Lennox-Gastaut syndrome •Tuberous Sclerosis Complex •Infantile Spasms

Medical Cannabis Patients in Colorado & Oregon in 2016



National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press. doi: 10.17226/4625.

THERAPEUTIC USES OF MEDICAL MARIJUANA: "DEBILITATING MEDICAL CONDITIONS" IN ALASKA

- Severe pain
- Persistent muscle spasms
- Cancer
- Glaucoma
- HIV/AIDS
- Seizures
- Cachexia
- Severe nausea

Therapeutic Uses Of Cannabis Or Cannabinoids National Academy Of Sciences Report

CONCLUSIVE or SUBSTANTIVE EVIDENCE	
Treatment of chronic pain in adults	Oral cannabinoids -nabiximols Inhaled cannabis
Improving patient-reported MS spasticity symptoms	Oral cannabinoids -nabiximols -dronabinol/nabilone -oral THC
Treatment of chemotherapy-induced NV	Oral cannabinoids -dronabinol/nabilone
MODERATE EVIDENCE	
Improving short-term sleep outcomes in individuals with sleep disturbance associated with OSA, fibromyalgia, chronic pain & MS	Cannabinoids -primarily nabiximols

National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press. doi: 10.17226/4625.

Therapeutic Uses Of Cannabis Or Cannabinoids National Academy Of Sciences Report

LIMITED EVIDENCE	
↑appetite/weight loss associated with HIV/AIDS	Inhaled cannabis Oral cannabinoids
Improving clinician-measured MS spasticity symptoms	Oral cannabinoids
Improving symptoms of Tourette Syndrome	THC capsules (2 studies)
Improving anxiety symptoms in social anxiety disorder	Cannabidiol (single study)
Improving symptoms of PTSD	Nabilone (single study)

National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press. doi: 10.17226/4625.

Therapeutic Uses Of Cannabis Or Cannabinoids National Academy Of Sciences Report

LIMITED EVIDENCE that is INEFFECTIVE	
Improving symptoms associated with dementia	Cannabinoids
Improving IOP associated with glaucoma	Cannabinoids
Reducing depressive symptoms in individuals with chronic pain or MS	Oral cannabinoids -nabiximols -dronabinol -nabilone

National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press. doi: 10.17226/4625.

Therapeutic Uses Of Cannabis Or Cannabinoids National Academy Of Sciences Report

NO or INSUFFICIENT TO SUPPORT OR REFUTE	
Cancer	ALS
Cancer-associated anorexia	Huntington's disease
Epilepsy	Dystonia
Irritable bowel syndrome	Achieving abstinence in substance abuse
Parkinson's Disease	Mental health outcomes in schizophrenia
Spasticity in paralysis d/t spinal cord injury	

National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press. doi: 10.17226/24025.

Acute Adverse Effects Of Marijuana

TOXIC REACTIONS (as seen in overdose/accidental ingestion by children)	
CNS	CARDIOVASCULAR
Anxiety	Tachycardia
Hallucinations	Chest pain
Panic episodes	RESPIRATORY
Drowsiness/lethargy	Respiratory depression
Ataxia	GASTROINTESTINAL
Confusion	NV
Seizures	Abdominal pain
Coma	

Acute Adverse Effects Of Marijuana: Accidental Ingestion By Children



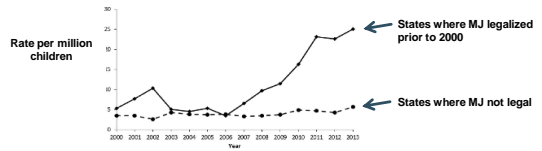
From www.legalmarijuanadispensary.com

NON-EDIBLE



From www.drugstore.com

Annual Rate Of Marijuana Exposure Among Children Younger Than 6 Years (National Poison Data System 2000-2013)



- Mean age 1.81 years
- 75% exposed through ingestion
- 18.5% required admission

Clin Pediatrics. 2016;55(5):428-436.

Acute Adverse Effects Of Marijuana

CNS EFFECT:	CARDIAC EFFECTS	DOSE RELATED IMPAIRMENT OF:
Anxiety	Tachycardia	Reaction time
Panic reactions	Orthostatic hypotension	Information processing
Psychotic symptoms		Perceptual-motor coordination
Sedation		Motor performance
Dizziness		Attention
Confusion		Tracking behavior



•IMPAIRED ABILITY TO DRIVE
•INCREASED RISK CRASHES

Chronic Adverse Effects Of Marijuana

DEPENDENCE	RESPIRATORY (if smoked)	CNS
Risk: 1 in 10 of long-term users	Chronic bronchitis	Memory/cognitive impairment
Risk: 1 in 6 of adolescent users	↓ pulmonary function	Psychotic symptoms/disorders
Risk: 1 in 2-3 of daily users	Pulmonary infections	OTHER
	Precancerous lesions	Cannabinoid hyperemesis syndrome

Potential Contaminants in Cannabis

- Aspergillus fungus, bacteria
- Aluminum, cadmium
- Pesticides
- Glass beads/sand
- Other psychotropic substances

Potential Drug-drug Interactions (From Published Clinical Evidence)

Increased CNS depressant effect	Increased THC effect	Increased concomitant drug effect	Decreased concomitant drug effect
Alcohol Phenytoin CNS depressants: Opioids Benzodiazepines Sedative hypnotics Barbiturates Antihistamines Muscle relaxants	Disulfiram Ketoconazole	Clozapine Hydrocortisone Phenytoin Warfarin Clobazam*	Clozapine Indinavir Phenytoin Theophylline
		THC metabolized by CYP3A4 and CYP2C9 CBD metabolized by CYP3A4 and CYP2C19	

From: Monitoring Health Concerns Related to Marijuana in Colorado: 2014 (<https://www.colorado.gov/pacific/cdpha/retail-marijuana-public-health-advisory-committee>)
*Epilepsia. 2015;56(9):1248-51.

CHALLENGES

- Marijuana use is deemed illegal by the federal government
- Medical marijuana production/manufacturing is not well regulated
- Doses of cannabinoids in marijuana products varies widely and may not be consistent
- Most marijuana research is in people who smoked for recreational use
- Most research regarding medical use of marijuana has been with cannabis-derived pharmaceuticals
- Scientific evidence to support the use of edible and topical forms of medical marijuana are lacking

CLINICAL APPLICATION: HARM REDUCTION

- Document use of medical marijuana in the medical record
- Counsel on variability of quality and concentration of medical marijuana
- Counsel patients on delayed time to effect after ingestion of oral marijuana
- Counsel patients on adverse effects; caution falls/fractures
- Counsel on potential drug interactions particularly CNS depressants/EtOH
- Advise patients not to drive after using medical marijuana
- Warn of risk of accidental ingestion in children/pets and to keep medical marijuana away from children/pets

Selected References

- Arshad MM, Carter DM, Shogrin N, et al. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. *J Pain*. 2016;17(12):1201-10.
- Bergel LM, Fanson KL, Nassbaum AM, Wang G. The pharmacologic and clinical effects of medical cannabis. *Pharmacotherapy*. 2013;33(2):195-209.
- Bonnick JM. Blurred boundaries: the therapeutics and politics of medical marijuana. *Mayo Clinic Proc*. 2012;87(2):172-86.
- Cohen P. Medical marijuana: the conflict between scientific evidence and political ideology. Part one of two. *J Pain Pall Care*. 2009;23(1):4-20.
- Cohen P. Medical marijuana: the conflict between scientific evidence and political ideology. Part two of two. *J Pain Pall Care*. 2009;23(2):120-40.
- Degehorst L, Hall W. The adverse effects of cannabinoids: implications for use of medical marijuana. *Can Med Assoc J*. 2008;178(13):1685-6.
- DeLuypens A, Mulla-Qasim A, Zohary N, Laska S. Efficacy and adverse effects of medical marijuana for chronic noncancer pain. *Clin Fam Physician*. 2015;61:4372-81.
- Dronovs C, March E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol*. 2016;15:270-79.
- Friedman D, Devinsky O. Cannabidiols in the treatment of epilepsy. *NEJM*. 2015;373:1348-58.
- Gatson TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. *Epilepsy Behav* (2016). <http://dx.doi.org/10.1016/j.yebeh.2016.11.016>
- Goffing ML, Falck SF, Bove PA, Thiele E. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia*. 2015;56(8):1246-51.
- Gloss D, Vasey B. Cannabinoids for epilepsy. *Cochrane Database Syst Rev*. 2014;3:CD009270.
- Hall W. The adverse health effects of cannabis use: what are they, and what are their implications for policy? *International J Drug Policy*. 2009;20:458-66.
- Hall W, Degehorst L. Adverse health effects of non-medical cannabis use. *Lancet*. 2003;361:1383-91.
- Heestkamp A, Heestkamp ER. The prevalence and incidence of medical cannabis on prescription in the Netherlands. *Eur J Clin Pharmacol*. 2013;69:1575-1580.
- Heestkamp A, Wiers MA, Mulder-Vaah KR, et al. The medicinal use of cannabis and cannabinoids—an international cross-sectional survey on administration forms. *J Psychoactive Drugs*. 2014;45:199-210.
- Health Canada. Information for Health Care Professionals—Cannabis and the cannabinoids (2013).
- Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems. *JAMA*. 2015;313(24):2474-2483.

Selected References

- Horn JR, Hester PD. Drug interactions with marijuana. *Pharmacy Times*. 2014;Dec:36.
- Kirby H, Mazer S. Anticipated medical effects on children from legalization of marijuana in Colorado and Washington state: a poison-center perspective. *JAMA Pediatrics*. 2013;167(7):602-3.
- Koppas BS, Boyd JC, Fu Y, et al. Systemic review, efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2014;82:1559-63.
- Leung J. Cannabis and its derivatives: review of medical use. *J Am Board Fam Med*. 2011;24(4):452-62.
- Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain: a systematic review of randomized trials. *BMJ*. 2011;70(25):735-44.
- Martin-Sanchez E, Faulkner T, Taylor J, Martin J. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med*. 2009;10(9):1363-65.
- McLaren J, Smith W, Olson P, Altaba S. Cannabis potency and consumption: a review of the literature. *Addiction*. 2008;103:1100-9.
- Medical marijuana and the mind. *Harvard Mental Health Letter*. 2010;26(10).
- Moore TM, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*. 2007;370:319-29.
- National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press. DOI: 10.17722/2542-0122
- Owens B, Casavant M, Spiller RK, et al. Marijuana exposure among children younger than six years in the United States. *Clin Pediatrics*. 2016;55(5):828-36.
- Vasey B, Rubin JC, Rubin ME, et al. Cannabinoid dose and diol accuracy in edible medical cannabis products. *JAMA*. 2015;313(24):2481-2483.
- Wang G, Rossenow G, Heard K. Pediatric marijuana exposures in a medical marijuana state. *JAMA Pediatrics*. 2013;167(7):630-3.
- Wang G, Rossenow G, Li Lal M, et al. Association of recreational/pediatric exposures with decarboxylation of marijuana in the United States. *Ann Emerg Med*. 2014;63:1460-6.
- Wang T, Collier J, Shroyer S, Wang M. Adverse effects of medical cannabinoids: a systematic review. *Can Med Assoc J*. 2008;178(13):1688-78.
- Whiting PF, Wolff RF, Doustans S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313(24):2468-2473.