Marijuana as Medication?
Reviewing Cannabis in the Treatment of Pain

Ryan Popp, Pharm.D.
PGY-1 Pharmacotherapy Resident
Controversies in Clinical Therapeutics
University of the Incarnate Word Feik School of Pharmacy
San Antonio, TX
March 23, 2018

Learning Objectives:

1. Describe the pharmacological attributes of cannabis.
2. Summarize the current state of cannabis use in the United States.
3. Examine the effectiveness of cannabis for the treatment of pain.
4. Evaluate the role of cannabis as a potential harm reduction strategy.

The Pharmacological Attributes of Cannabis

What is Cannabis?

- Cannabis, or marijuana, is an plant that has been used for its recreational and medicinal purposes for over 2000 years[1]
- Commonly referred to as "weed," "Mary Jane," "dope," or "pot"[2]
- Most commonly used illicit substance in the United States, with 22.2 million people who use it[3]
    - 11 million people who use cannabis are emerging adults (ages 18-25)[2]
- Worldwide prevalence of use is approximately 3.8%[4]

Key Terms:[5]

- Cannabis: Of or referring to marijuana and its constituent ingredients
    - Marijuana: Whole, unprocessed cannabis plant or its basic extracts
    - Cannabinoids: Biologically active compounds found in marijuana
- Marijuana:
    - Medical Use: use for symptomatic treatment of illness
    - Recreational Use: use apart from medical purposes
- Cannabinoids:
    - Natural: any of the 70+ active compounds in marijuana
    - Pharmaceutical Grade: refined cannabinoids (such as CBD or THC) for inclusion in a drug product

What is in Cannabis?

- Cannabis contains over 70 active compounds, called cannabinoids[6]
- The primary compounds are THC and CBD[1,6,7]
    - THC (Δ^9-tetrahydrocannabinol) is the primary psychoactive agent in cannabis, and causes the following effects:

Mild Euphoria	Analgesia	Sedation/Relaxation
Hunger	Enhanced Sensory Input	Impaired attention, balance, cognition, judgment, memory, or sense of time

    - CBD (cannabidiol) antagonizes the psychotropic effects of THC while also increasing the activity of the endogenous cannabinoid system, leading to the following effects:

Analgesia	Anti-inflammatory activity	Mitigation of psychotropic THC effects (CBD has no euphoria or intoxication effects on its own)

- THC:CBD Ratio[7]
    - The ratio of THC to CBD is a partial determinant of patient response
    - Ratio of THC to CBC can vary by:

Geographic Origin	Parts of Plant Used (buds/stem/seeds)
Storage Methods	Cultivation Techniques

The Endocannabinoid System (ECS):[6-10]

- The ECS can be summarized by the actions "relax, sleep, eat, protect, and forget"[11]
- THC and CBD act on a variety of receptors, of which the cannabinoid-type 1 (CB1) and type 2 (CB2) receptors are well characterized

	CB1	CB2
Endogenous Ligands	Anandamide (arachidonoyl ethanolamine [AEA]) 2-arachidonoylglycerol (2-AG)	
Exogenous Ligands	THC, CBD, and other cannabinoids	
Locations	• Central Nervous System ○ Notable exception: brainstem, medulla, thalamus • Peripheral Nervous System • Ubiquitous presentation in most organs including (testis, eye, vascular endothelium, spleen, myocardium, skeletal muscle, bone, skin, kidney, and GI tract)	• Immune System Cells • Central Nervous System • Bone • Liver
Activity	Suppression of both glutaminergic (excitatory) and GABAergic (inhibitor) pathways	Suppression of inflammatory mediators
Therapeutic Effects	• Nociception suppression • Dissociation of emotional component of pain	• Desensitization of pain receptors • Anti-inflammatory activity

Cannabis Types:

- Marijuana:[1,6]
  - Preferred mode of administration among people who use cannabis[12]
  - Two main strains of marijuana:

Sativa: Tall, long leaves, grows outdoors	*Indica*: Bushy, short leaves, grows indoors

    - Mixing strains results in differing THC:CBC ratios
  - Botanical Formulations:
    - Herbal form consists of flowering tops, leaves, and stalks of the mature plant
    - Hash consists of the resinous extract of compressed herb
  - Increasing Potency:[4,13]
    - Average THC potency of leaf marijuana rose from 3.96% (1995) to 12.55% (2013)
    - Average THC content of hash oil rose from ~16% (1990s) to 52% (2013)
- Pharmaceutical-Grade Cannabinoids:[14]

	Dronabinol	*Nabilone*	*Nabiximols*	*Epidolex*
Ingredient	THC	Synthetic THC derivative	Equal concentrations of THC and CBD	CBD
Formulation	Capsules	Capsules	Oromucosal Spray	Oral Liquid
FDA Indications	- Chemotherapy-induced nausea - Appetite stimulation in patients with AIDS	- Chemotherapy induced nausea - Anorexia - Weight loss in patients with AIDS	- IND status for the treatment of cancer pain	- IND status for the treatment of intractable seizure syndromes in children

- Synthetic Analogues of Marijuana:[1,4]
  - Termed "K2," "Spice," "Mr. Smiley," "Black Mamba," "Red X Dawn," "Blaze," "Dream"
  - Not easily tested by drug screens
  - Produces effects similar to marijuana, with additional sympathomimetic symptoms such as severe agitation and anxiety, extreme tachycardia, hypertension, nausea and vomiting, spasms, seizures, tremors, diaphoresis, and restlessness
  - Not recommended due to potential of life-threating side effects

Marijuana Administration:[14]

- Inhalation Methods: Preferred administration route for 80% of people who use marijuana[2,11,15]

Hand-rolled cigarettes (*joints*)	Pipes or water pipes (*bongs*)
Marijuana cigars (*blunts*)	Vaporizers

- Oral Methods:[2,11]

Mixed with food (edibles)	Extracted resin (hash)

- Pros/Cons:

	Inhalation	*Oral*
Advantages[14]	• Fast Onset (1-10 minutes) • Easily self-titratable	• Non-complicated administration • Lower abuse risk
Disadvantages[14]	• Inhalation of toxic combustion products • Variable efficacy due to differences in inhalation techniques (puff frequency, inhalation depth, and smoke retention)	• Poor bioavailability • Slow, erratic, variable absorption • Psychoactive metabolites from liver —> increased side effects

Formulation-Specific Challenges of Cannabis:[1]

- Inhalation Technique:
  - Amount of cannabinoids delivered to the alveoli varies depending on individual inhalation/exhalation technique and functional lung capacity
- Quality Control:
  - Lack of standardization of medical marijuana can result in variable therapeutic efficacy and side effects
- Contaminants in Cannabis:
  - Biological contaminants (e.g., bacteria and *Aspergillus* fungus)
  - Heavy metals from soil (e.g., aluminum and cadmium)
  - Organophosphate pesticides for cannabis grown outdoors
  - Tiny glass beads or sand have been found in street samples of cannabis in order to boost weight and profits

The Current State of Cannabis Use in the United States

Regulation of Cannabis:[1,7]

- Federal Laws:
  - Controlled Substance Act - 1970
    - Classified marijuana as a Schedule I controlled substance
    - Penalizes any act of cultivating, possessing, dispensing, or prescribing marijuana
  - Federal Enforcement[16]

The Cole Memo (2013)	The Sessions Memo (2018)
Indicated that while marijuana remained illegal federally, the Department of Justice would defer the right to challenge legalization laws so long as states strongly enforced the following eight federal interests: 1. Preventing the distribution of marijuana to minors 2. Preventing revenue from the sale of marijuana from going to criminal enterprises, gangs, and cartels 3. Preventing the diversion of marijuana from states where it is legal under state law to other states 4. Preventing state-authorized marijuana activity from being used as a cover or pretext for the trafficking of other illegal drugs or other illegal activity 5. Preventing violence and the use of firearms in the cultivation and distribution of marijuana 6. Preventing drugged driving and other adverse public health consequences associated with marijuana use 7. Preventing the growing of marijuana on public lands and the attendant public safety and environmental dangers posed by marijuana production on public lands 8. Preventing marijuana possession or use on federal property	Rescinded the Cole Memo and instructed federal prosecutors to decide on how to prioritize enforcement of federal marijuana in light of the following considerations: 1. Current law enforcement priorities 2. Seriousness of the crime 3. Deterrent effect of criminal prosecution 4. Cumulative impact of particular crimes on the community

- State Level Legalization:[16,17]
  - 29 states and the District of Columbia have passed comprehensive public medical marijuana and cannabis programs. Such programs consist of the following:
    1. Protection from criminal penalties for using marijuana for a medical purpose
    2. Access to marijuana through home cultivation, dispensaries or some other system that is likely to be implemented
    3. It allows a variety of strains, including those more than “low THC”, and
    4. It allows either smoking or vaporization of some kind of marijuana products, plant material or extract
  - 8 of the above states and the District of Columbia have legalized recreational use of marijuana, meaning that it can be used by adults regardless of medical need
  - 17 states (including Texas) have limited use marijuana laws which permit use of “low THC, high cannabidiol (CBD)” products for medical reasons in limited situations or as a legal defense

Who is Using Cannabis?[15,18-22]

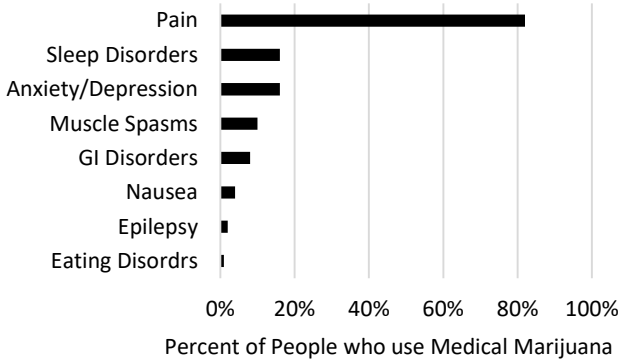
- People who are registered to use cannabis for medical purposes (2.5 million registered people) make up a small fraction of all people who use cannabis for non-medical purposes (22.2 million people)
- However, 86% of individuals who use marijuana medically also use it recreationally, blurring the distinction between medical and recreational use

- Typical person who uses medical cannabis:

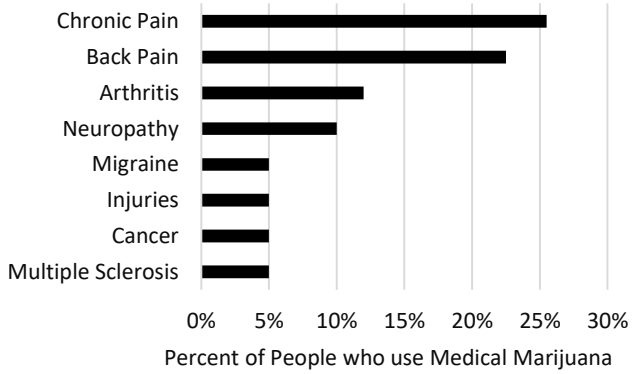
More Likely to be…	Less Likely to be…
o White or African American (versus Hispanic or Asian) o Male o 25-54 years of age o Employed with Health Insurance o People who use tobacco	o People who use alcohol o People who use cocaine o College degree holders

Demographics of Cannabis Use[15,18-20]

Medical Conditions Treated with Cannabis

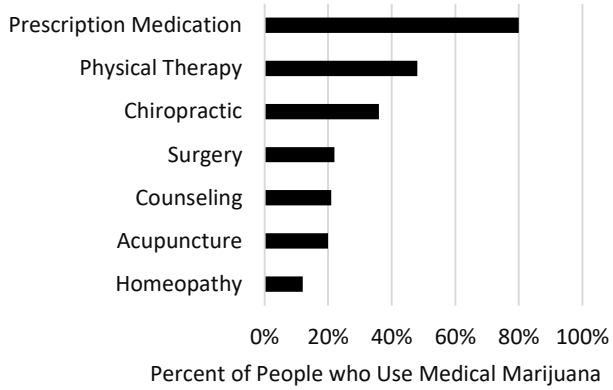


Types of Pain Treated with Cannabis

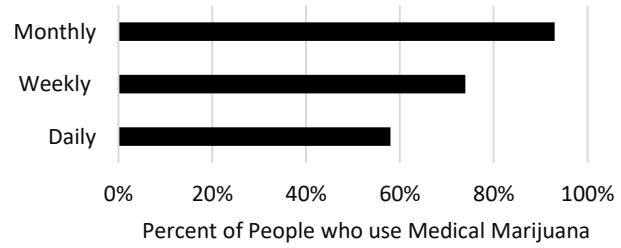


- According to state registries:[7]
  - 89% of people who use medical cannabis in Arizona and 94% of people who use medical cannabis in Colorado are registered for severe or chronic pain

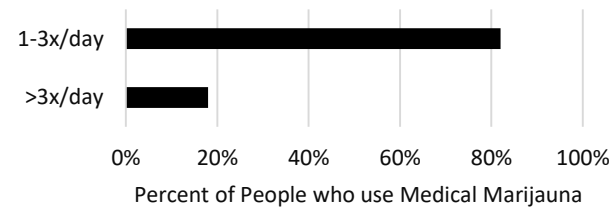
Other Treatment Modalities Tried for the Medical Conditions Treated by Medical Marijuana

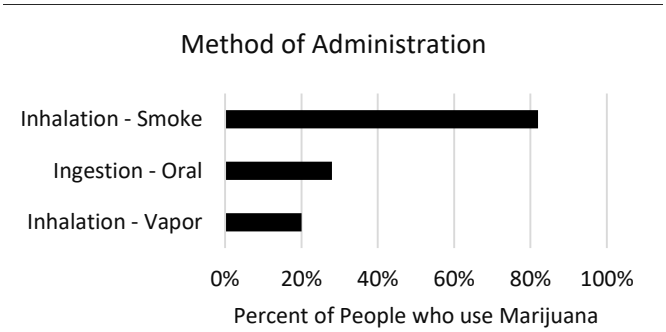


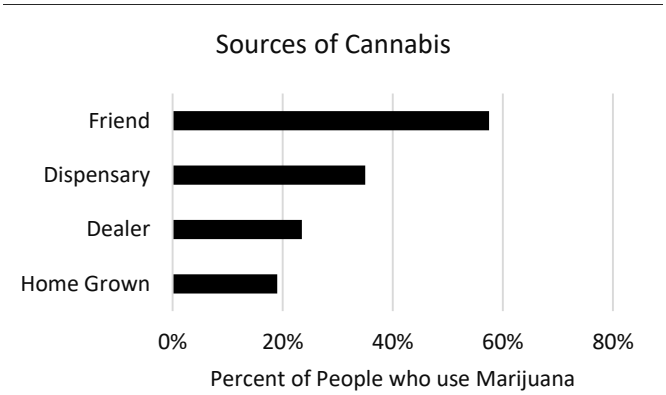
Frequency of Medical Marijuana Use

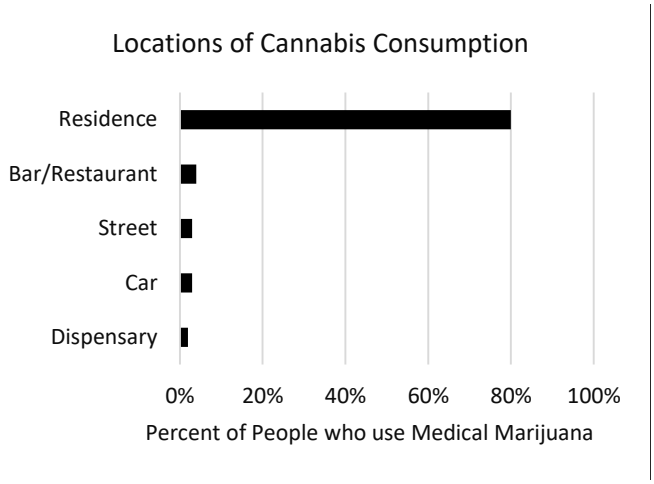


Times per Day of Medical Marijuana Use









What does it Take to Obtain Legal Marijuana?[16]

- Most states require enrollment in a patient registry and the provision of ID cards in order to obtain medical marijuana. Patients generally must specify which condition they are treating with the marijuana.
- In addition, most states allow dispensaries for the distribution of medical marijuana

The Effectiveness of Cannabis for the Treatment of Pain

Types of Pain:[23]

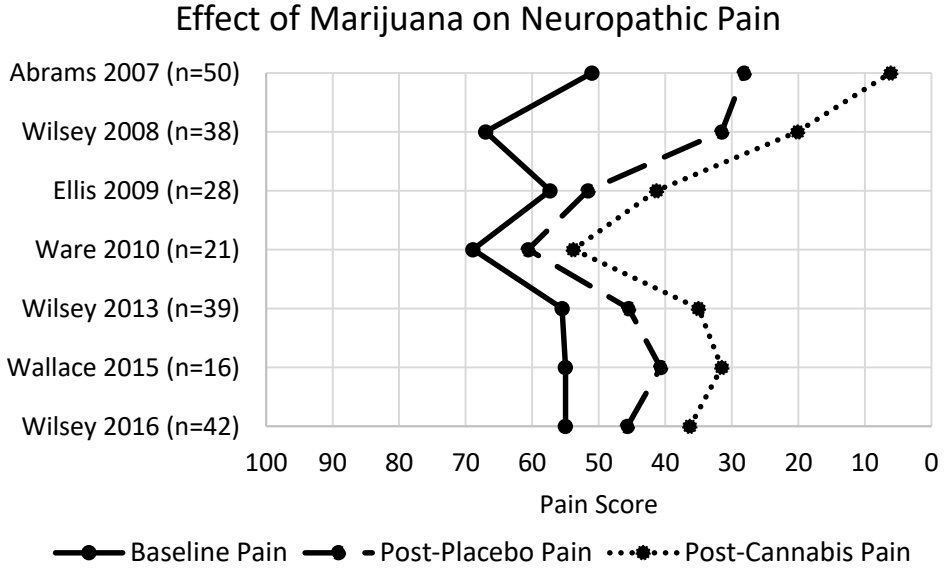
- Nociceptive pain: pain related to damage of somatic or visceral tissue due to trauma or inflammation
    - Examples: arthritis, gout, neck and back pain, sickle cell disease, inflammatory bowel disease
- Neuropathic pain: pain related to damage of peripheral or central nerves
    - Examples: diabetic neuropathy, chemotherapy-induced neuropathy, persistent postoperative pain, multiple sclerosis pain, post-herpetic neuralgia
- Sensory hypersensitivity: pain without identifiable nerve or tissue damage thought to result from persistent neuronal dysregulation
    - Examples: fibromyalgia, irritable bowel syndrome, tension headaches, restless leg syndrome, chronic fatigue syndrome

Barriers to Assessing the Literature of Cannabis:[1,7]

1. Inconsistent classification and definitions of different levels of cannabis use (i.e., heavy, regular, occasional, and non-users)
2. Variable study quality regarding trial design, control of confounding variables
3. Polarization of study approach, comparing either non-users to light users or comparing light/non-dependent users to heavy/dependent users

Treatment of Neuropathic Pain:

- There are seven randomized controlled trials (RTCs) which evaluate the efficacy of marijuana in neuropathic pain secondary to HIV, diabetes, spinal cord injury, and trauma/surgery.
- Findings of RTCs: Inhaled cannabis demonstrated a consistent benefit over placebo alone for the treatment of neuropathic pain. High-potency (higher THC) cannabis trended towards greater effectiveness compared to low-potency.



- Most common side effects were neurocognitive impairment, sedation, dizziness, confusion, and hunger. Occurrence of tachycardia and anxiety side effects were variable within the studies.

RTCs Assessing the Efficacy of Marijuana in Neuropathic Pain			
Study	Population	Intervention	Outcomes

Abrams et al.[24] (2007)	• Prospective, randomized, double-blind, randomized, placebo-controlled trial (n=50)
	• Adults with painful HIV-associated sensory neuropathy receiving treatment with other analgesics and who have previously used cannabis
		• Cannabis cigarette (3.56% THC) three times a day for 5 days
		• Placebo cigarette (0% THC)
		• Background medications were continued
			• Baseline Visual Analog Pain Scale (VAS) Score (out of 100):
			  • Cannabis: 52 (IQR 38-71)
			  • Placebo: 57 (IQR 40-74)
			• VAS Reduction:
			  • Cannabis: 34% (p=0.03)
			  • Placebo: 17%
			• Percent of Patients with 30% reduction in pain scores:
			  • Cannabis: 52% (p<0.001)
			  • Placebo: 24%
			• Cannabis Side Effects:
			  • Mild increase in sedation, anxiety, confusion, and dizziness

Wilsey et al.[25] (2008)	• Prospective, crossover, double-blind, randomized, placebo-controlled trial (n=38)
	• Adults with central and peripheral neuropathic pain who have previously used cannabis
		• High-dose cannabis cigarette (7% THC), 9 puffs over a 3 hour period
		• Low-dose cannabis cigarette (3.5% THC)
		• Placebo cigarette (0% THC)
		• Background medications were continued
			• Baseline VAS Score (out of 100):
			  • All patients: 55 (SD 21)
			• VAS Reduction:
			  • High-dose and low-dose cannabis: 43% (p=0.02)
			  • Placebo: 26%
			• Cannabis Side Effects:
			  • Neurocognitive impairment in attention, learning and memory, and psychomotor speed was significant in the high-dose group
			  • Both potencies had sedation, confusion, and hunger

Ellis et al.[26] (2009)	• Prospective, crossover, double-blind, randomized, placebo-controlled trial (n=28)
	• Adult patients with HIV-associated sensory neuropathy with at least 2 previous analgesics
		• Cannabis cigarette (1-8% THC), four times a day for 5 days, strength titrated to efficacy and tolerability
		• Placebo cigarette (0% THC)
		• Background medications were continued
			• Baseline Descriptor Differential Scale (DDS) pain score (out of 20):
			  • All patients: 11.1 (IQR 9.1-13.7)
			• DDS Reduction:
			  • Cannabis: 37% (p=0.029)
			  • Placebo: 1%
			• Percent of Patients with 30% reduction in pain scores:
			  • Cannabis: 46% (p=0.043)
			  • Placebo: 18%
			• Cannabis Side Effects:
			  • Tachycardia, concentration difficulties, sedation, reduced salivation, and thirst

RTCs Assessing the Efficacy of Marijuana in Neuropathic Pain			
Study	Population	Intervention	Outcomes

Ware et al.[27] (2010)	• Prospective, crossover, double-blind, randomized trial (n=21)
	• Adult patients with post-traumatic or post-surgical neuropathic pain receiving treatment with other analgesics
		• Smoked cannabis (via pipe) at four potencies (0%, 2.5%, 6%, and 9.4%) inhaled three times daily for 5 days, followed by a 9 day washout period
		• Background medications were continued
			• Baseline pain intensity according to 11-item numeric rating scale:
			  • All patients: 6.89 (SD 1.27)
			• Reduction in pain intensity according to 11-item numeric rating scale:
			  • Cannabis (9.4% THC): 22% ($p<0.05$)
			  • Placebo: 12%
			  • Other cannabis potencies had no significant reduction
			• Cannabis Side Effects:
			  • Drowsiness, headache, dry eyes, dizziness, numbness, and cough

Wilsey et al.[28] (2013)	• Prospective, crossover, double blind, randomized, placebo controlled trial (n=39)
	• Adult patients with neuropathic pain who have previously used cannabis
		• Medium-dose vaporized cannabis (3.53% THC) 8-12 puffs over a 3 hour period
		• Low-dose vaporized cannabis (1.29% THC)
		• Placebo vaporized cannabis (0% THC)
		• Background medications were continued
			• Baseline VAS Score (out of 100):
			  • Med-dose cannabis: 57.3 ± 24.1
			  • Low-dose cannabis: 53.4 ± 23.4
			  • Placebo: 57.4 ± 22.8
			• VAS Reduction:
			  • Med-dose cannabis: 28% ($p<0.01$)
			  • Low-dose cannabis: 23% ($p<0.01$)
			  • Placebo: 10%
			• Percent of Patients with 30% reduction in pain scores:
			  • Med-dose cannabis: 61% ($p<0.01$)
			  • Low-dose cannabis: 57% ($p<0.01$)
			  • Placebo: 30%
			• Cannabis Side Effects:
			  • Sedation, hunger, and neurocognitive impairment

Wilsey et al.[29] (2016)	• Prospective, crossover, double blind, randomized, placebo controlled (n=42)
	• Adult patients with neuropathic pain related to injury or disease of the spinal cord
		• Vaporized cannabis (either 2.9% or 6.7% THC) 8-12 puffs over a 4 hour period
		• Placebo
		• Background medications were continued
			• Baseline pain intensity according to 11-item numeric rating scale:
			  • Cannabis groups: 5.2 (SD 2.1)
			  • Placebo group: 5.0 (SD 1.8)
			• Percent of Patients with 30% reduction in pain scores:
			  • High-dose cannabis: 88% ($p<0.001$)
			  • Low-dose cannabis: 70%
			  • Placebo: 45%
			• Cannabis Side Effects:
			  • No neurocognitive effects

RTCs Assessing the Efficacy of Marijuana in Neuropathic Pain			
Study	Population	Intervention	Outcomes

Wallace et al.[30] (2015)	• Prospective, crossover, double blind, randomized, placebo controlled (n=16)
	• Adult patients with painful diabetic peripheral neuropathy
		• Aerolized cannabis (low-dose (1% THC), medium-dose (4%), or high-dose (7%)), three inhalations within a 3 minute period
		• Placebo
		• Background medications were continued
			• Baseline spontaneous pain score using numeric pain rating scale (out of 10):
			  • All patients: 6.7 (SD 1.6)
			• Pain Score Reduction:
			  • High-dose cannabis: 70% ($p<0.05$)
			  • Med-dose cannabis: 65%
			  • Low-dose cannabis: 64%
			  • Placebo: 53%
			• Percent of Patients with 30% reduction in pain scores:
			  • High-dose cannabis: 81%
			  • Med-dose cannabis: 80%
			  • Low-dose cannabis: 67%
			  • Placebo: 62%
			• Cannabis Side Effects:
			  • Somnolence and euphoria

Multiple Sclerosis Spasticity-related Pain:

- There is 1 RTC which evaluates the efficacy of marijuana in treating spasticity and pain secondary to multiple sclerosis (MS)
- Findings of RTC: Cannabis was more effective than placebo at reducing MS spasticity and pain

RTCs Assessing the Efficacy of Marijuana in Multiple Sclerosis Spasticity-related Pain			
Study	Population	Intervention	Outcomes

Corey-Bloom et al.[31] (2012)	• Prospective, crossover, double-blind, randomized, placebo controlled trial (n=30)
	• Adult patients with multiple sclerosis and spasticity
		• Cannabis cigarettes (4% THC), once daily for 3 days followed by an 11 day washout period
		• Placebo cigarettes
		• Background medications were continued
			• Baseline VAS Score (out of 100):
			  • Cannabis: 16.2 (95% CI 10.8-24.9)
			  • Placebo: 14.5 (95% CI: 9.2-21.8)
			• VAS Reduction (% from baseline):
			  • Cannabis: 50%
			  • Placebo: 21%
			• Cannabis Side Effects:
			  • Dizziness and fatigue

Other Pain Types:

- There are no other trials which assess the efficacy of marijuana for the treatment of nociceptive pain or sensory hypersensitivity
- Although there has been research on pharmaceutical-grade cannabinoids in the treatment of various types of pain, the generalizability of these studies to traditional marijuana use is limited by the following factors:
  1. Pharmaceutical-grade cannabinoids have different administration routes
  2. Pharmaceutical-grade cannabinoids generally contain only one cannabinoid (THC or CBD), and therefore do not mirror the blend of cannabinoids present in botanical marijuana

The Role of Cannabis as a Harm Reduction Strategy

Harm Reduction

- Harm reduction is that which reduces the negative consequences associated with human behaviors

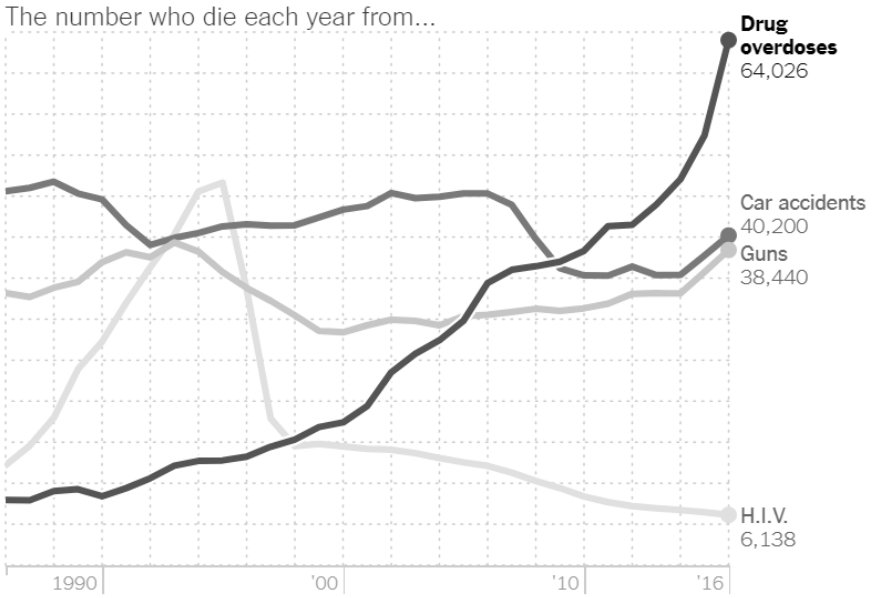
Harm Reduction Strategy	Benefits
Seatbelts	Reduces risk of serious trauma from automobile accidents
Syringe Service Programs	Reduces risk of infectious disease transmission in people who use IV drugs recreationally
Condoms	Reduces risk of pregnancy and sexually transmitted infections

Opioid Epidemic

- By the numbers:[32-37]

116 million	American adults affected by chronic pain in 2011
259 million	Prescriptions for pain relievers written in 2012
42,000	People who died from opioid overdose in 2016
$78.5 billion	Economic cost of opioid epidemic in 2013
#1 Cause of Death	Opioid overdose mortality in adults < 50 years of age

- Cause of Death Chart:[33]



- Why does it matter?[38]
  - There is a clinical need for safe, effective, and non-addicting medications as an alternative for opioids in the management of chronic pain
  - 6-39% of patients using opioid pain relievers also use cannabis[39]
  - Over 80% of people who use medical marijuana report using cannabis for relief of pain[20]
  - Cannabinoids do not produce respiratory depression, and the lethal dose is between 15-70 grams, which is several times the amount that can be consumed in a day

Ecological Studies Examining the Effect of Medical Marijuana Laws on State-Level Outcomes:

- In 2012, Cerda and colleagues reported that the prevalence of marijuana use was higher in states *with* medical marijuana laws (MMLs) versus states *without* MMLs[40]

	Prevalence of *past-year marijuana use in 2005*		
Data Source	States with MMLs	States without MMLs	p value
NESARC: conducted via face-to-face interviews	7.13%	3.57%	p<0.0001
NSDUH: conducted via self-administration	12.17%	9.77%	p=0.0006
NESARC = National Epidemiologic Survey on Alcohol and Related Conditions NSDUH = National Survey on Drug Use and Health			

- In 2014, Bachhuber and colleagues used state level data to determine that medical marijuana laws were associated with a decrease in opioid overdose mortality

Bachhuber et al (2014)[41] Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010	
Objective	To determine the association between the presence of state medical marijuana laws (MMLs) and opioid analgesic overdose mortality
Methods	
Design	Time-Series Analysis and Retrospective Database Review
Hypothesis	a) Increased access to medical cannabis may reduce opioid use, reducing opioid overdose b) Increased access to medical cannabis may lead to further substance abuse, increasing the rate of drug overdose
Procedures	• Opioid overdose mortality data was obtained from the Wide-ranging Online Data for Epidemiologic Research (WONDER) dataset published by the CDC • Data was modeled to compare the opioid overdose mortality rate before and after MMLs • Primary Independent Variables: State; Year; Presence of MML • Secondary Independent Variables: Presence of prescription drug monitoring program; Presence of laws requiring patient ID before dispensing; Presence of regulations for increased state oversight of pain clinics; State- and year- specific unemployment rates
Population	• All 50 states of the United States
Outcomes	• Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a MML
Statistical Analysis	• Linear time-series regression models were used to determine the association between MMLs and opioid analgesic-related deaths

	• Sensitivity Analyses:
	  ○ Exclusion of intentional (suicide) overdose deaths
	  ○ Inclusion of all heroin overdose deaths (even w/o prescription opioid)
	• Specificity Analyses:
	  ○ Examined the association between state MMLs and death rates of heart disease and septicemia (conditions without strong links to cannabis use)

Results	

Study Outcomes	Percentage difference in age-adjusted opioid overdose mortality in states with versus without MMLs:
	• Overall Difference: **-24.8%** (95% CI, -37.5% to -9.5%; p≤0.05)
	• Difference according to years prior to passage of MMLs:
	  ○ 2 years prior: -13.1% (95% CI, -45.5% to 38.6%; p=0.56)
	  ○ 1 year prior: 1.2% (95% CI, -41.2% to 74.0%; p=0.97)
	• Difference according to years following passage of MMLs:
	  ○ 1 year after: **-19.9%** (95% CI, -30.6% to -7.7%; p=0.002)
	  ○ 2 years: **-25.2%** (95% CI, -40.6% to -5.9%; p=0.01)
	  ○ 3 years: **-23.6%** (95% CI, -41.1% to -1.0%; p=0.04)
	  ○ 4 years: **-20.2%** (95% CI, -33.6% to -4.0%; p=0.02)
	  ○ 5 years: **-33.7%** (95% CI, -50.9% to -10.4%, p=0.008)
	  ○ 6 years: **-33.3%** (95% CI -44.7% to -19.6%; p≤0.001)
	• Sensitivity Analyses:
	  ○ Exclude intentional overdose deaths: **-31.0%** (95% CI, -42.2% to -17.6%; p≤0.001)
	  ○ Include heroin overdose deaths: **-23.1%** (95% CI -37.1% to -5.9%, p≤0.05)
	• Specificity Analyses:
	  ○ Association between MMLs and heart disease mortality: 1.4% (95% CI, -0.2% to 2.9%, p=0.09)
	  ○ Association between MMLs and septicemia mortality: -1.8% (95% CI, -7.6% to 4.3%, p=0.55)

Critique[42]	
Strengths	• Inclusion of sensitivity and specificity analyses strengthens the findings of this study • Demonstration of the change in opioid overdose mortality according to years following passage of MMLs strengthens the findings of this study
Limitations	• Ecologic analysis cannot account for individual characteristics, such as socioeconomic status, race/ethnicity, or medical diagnoses • Death certificate data may not correctly classify cases of opioid overdose deaths • There may be important time- and state- varying confounders that were not included in this study • Although this study shows a correlation between MMLs and opioid overdose mortality rates, a direct cause-effect relationship cannot be elucidated
Take Away Summary	
In states that passed medical marijuana laws (MMLs) between 1999 and 2010, there was a progressive decrease in the rate of opioid overdose mortality compared to states without MMLs	

- In 2015, Powell and colleagues used state level data to determine that medical marijuana dispensaries were associated with a decrease in opioid addiction as well as a decrease in opioid overdose mortality[43]

<table>
<tr><th colspan="2">Powell et al (2015)[43]
Do Medical Marijuana Laws Reduce Addictions and Deaths Related to Pain Killers?</th></tr>
<tr><td>Objective</td><td>To examine whether medical marijuana laws (MMLs) reduced prescription opioid misuse</td></tr>
<tr><th colspan="2">Methods</th></tr>
<tr><td>Design</td><td>Retrospective database review</td></tr>
<tr><td>Hypothesis</td><td>• If marijuana is an effective alternative to opioids, then states that provide legal access to marijuana may have a lower rate of opioid misuse</td></tr>
<tr><td>Procedures</td><td>• Data Sources:
○ Treatment Episode Data Set (TEDs): data on opioid-abuse treatment
○ National Vital Statistics System (NVSS): data on opioid-related deaths
○ Drug Enforcement Administration’s (DEA) Automation of Reports and Consolidated Orders System (ARCOS): supply of opioids through legitimate medical channels from manufacturers to retailers
• Data was modeled to compare states with MMLs versus those without MMLs
• Independent Variables:
<table>
<tr><td>Any MML</td><td>State Age Distribution</td></tr>
<tr><td>MML allowing marijuana dispensaries</td><td>State Population</td></tr>
<tr><td>Prescription Drug Monitoring Program factors</td><td>State Alcohol Tax</td></tr>
<tr><td>State % Male Population</td><td>State Unemployment Rate</td></tr>
<tr><td>State % White Population</td><td></td></tr>
</table></td></tr>
<tr><td>Population</td><td>• All 50 states of the United States</td></tr>
<tr><td>Outcomes</td><td>• Treatment admissions for addiction to pain relievers (1992-2012)
• State-level opioid overdose deaths (1999-2013)
• Distribution of opioids to states from manufacturers (2000-2011)</td></tr>
<tr><th colspan="2">Results</th></tr>
<tr><td>Study Outcomes</td><td>Comparison between states with versus states without the following:
<table>
<tr><th>Outcome</th><th>Presence of MML</th><th>Presence of Dispensary</th></tr>
<tr><td>Treatment admissions for addiction to pain relievers</td><td>No significant relationship</td><td>28% reduction</td></tr>
<tr><td>State-level opioid overdose deaths</td><td>No significant relationship</td><td>16% reduction</td></tr>
<tr><td>Distribution of opioids to states from manufacturers</td><td>No significant relationship</td><td>No significant relationship</td></tr>
</table></td></tr>
<tr><th colspan="2">Critique</th></tr>
<tr><td>Strengths</td><td>• Examined extra years of data (2011-2013) compared to Bachhuber et al
• Accounts for dispensaries in addition to presence of MML</td></tr>
<tr><td>Limitations</td><td>• Duration of observed effects is difficult to ascertain</td></tr>
<tr><th colspan="2">Take Away Summary</th></tr>
<tr><td colspan="2">It is access to medical marijuana via dispensaries, and not medical marijuana laws, that is associated with a decrease in opioid abuse (decrease in treatment admissions for addiction and decrease in opioid overdose mortality). The fact that there was no concurrent change in the amount of opioid distribution to states suggests that many abused opioids are procured outside of legal acquisition channels.</td></tr>
</table>

- In 2017, Shi and colleagues utilized state level data to determine that medical marijuana laws were associated with a decrease in the rate of hospitalizations for opioid dependence/abuse and opioid overdose[44]

<table>
<tr><th colspan="2">Shi et al (2017)[44]
Medical Marijuana Policies and Hospitalizations Related to Marijuana and Opioid Pain Reliever</th></tr>
<tr><td>Objective</td><td>To examine the association between state medical marijuana laws (MMLs) and hospitalizations related to marijuana and opioid pain relievers</td></tr>
<tr><th colspan="2">Methods</th></tr>
<tr><td>Design</td><td>Retrospective database review</td></tr>
<tr><td>Hypothesis</td><td>a) Increased access to medical marijuana may serve as a substitute to opioid pain relievers, reducing the risk of opioid related health consequences
b) Increased access to medical cannabis may serve as a gateway drug to opioid pain relievers and increase the risk of starting opioids and subsequent adverse effects</td></tr>
<tr><td>Procedures</td><td>• State-level administration data of hospital discharges from 1997 to 2014 was obtained from the State Inpatient Databases (SID)
• Data was modeled to assess the association between medical marijuana policies and various hospitalizations
• Independent Variables:
<table>
<tr><td>Marijuana decriminalization</td><td>Prescription monitoring programs</td></tr>
<tr><td>Pain management clinic regulations</td><td>Socioeconomic factors</td></tr>
<tr><td>State</td><td>Year</td></tr>
<tr><td>State Population Size</td><td>State Unemployment Rate</td></tr>
<tr><td>State Median Household Income</td><td>State Beer tax rate per gallon</td></tr>
<tr><td>Uninsured rate</td><td></td></tr>
</table></td></tr>
<tr><td>Population</td><td>• 27 States of the United States (all for which full data were available)</td></tr>
<tr><td>Outcomes</td><td>• Rates of hospitalizations involving either of the following:
○ Marijuana dependence or abuse
○ Opioid dependence or abuse
○ Opioid pain reliever overdose</td></tr>
<tr><th colspan="2">Results</th></tr>
<tr><td>Study Outcomes</td><td>• Difference in the rate of hospitalizations for the following reasons (between states with MMLs versus states without MMLs):
○ Marijuana dependence or abuse: No difference
○ Opioid dependence or abuse: -23% (p=0.008)
○ Opioid pain reliever overdose: -13% (p=0.025)</td></tr>
<tr><th colspan="2">Critique</th></tr>
<tr><td>Strengths</td><td>• Use of a previously published method to assess new outcomes</td></tr>
<tr><td>Limitations</td><td>• Variation between states in medical coding practices and inclusion of psychiatric and Veteran Affairs hospitals</td></tr>
<tr><th colspan="2">Take Away Summary</th></tr>
<tr><td colspan="2">Summary: Medical marijuana laws (MMLs) decrease the rate of hospitalization related to opioid abuse (either opioid dependence, abuse, or overdose). However, MMLs do not have an effect on the rate of hospitalizations for marijuana dependence or abuse.</td></tr>
</table>

Observational Studies Examining the Effect of Medical Marijuana Patient-Specific Outcomes:

Studies Examining the Effect of Marijuana on Controlled Substance Use

- Findings: Cannabis use generally serves as a substitute to prescription medications, especially opioids. This may explain the findings in the aforementioned ecological studies regarding the effect of medical marijuana laws on state-level outcomes.
- Limitations:
    - Recall data is potentially unreliable
    - Bias in favor of efficacy in marijuana group due to self-selected convenience samples
    - Variable survey response rate could influence results (potential responder bias)
    - It is difficult to quantify how much cannabis patients are using

Studies Assessing the Effect of Marijuana on Use of Prescription Drugs			
Study	Population	Methods	Outcomes
Kral et al.[45] (2015)	• 653 people who inject drugs were recruited from Los Angeles and San Francisco, California	• Interview survey was administered to measure the use of injectable drugs and marijuana	• Number of times opioids were used in past 30 days was significantly lower for people who used cannabis than those who did not use cannabis in the past 30 days (median 30 vs 60 times, respectively; p<0.003)

Boehnke et al.[46] (2016)	• 185 medical cannabis patients with chronic pain in Michigan	• Online survey was administered to assess changes in opioid use, quality of life, medication classes used, and medication side effects before and after initiation of cannabis use	• Following initiation of cannabis use…
			  ○ Mean change in self-reported opioid use was -64% (SD 45%)
			  ○ Quality of life increased by 45% (SD 29%)
			• Mean number of medication classes used decreased from 2.38 to 1.81 (p<0.001)

Lucas et al.[47] (2017)	• 271 patients who registered to purchase marijuana from a federally authorized licensed producer of cannabis in Canada	• Online survey which measured patient experiences, patterns of use, and cannabis substitution effects	• Patients reported using marijuana for pain (73%), stress (60%), insomnia (57%), depression (46%) and headache (32%) • 71% of patients reported substituting cannabis for other substances, with 63% reporting substitution for prescription medication, 25% for alcohol, 12% for tobacco, and 3% for illicit substances • Of patients that substituted cannabis for prescription medications, 32% did so for opioids, 16% did so for benzodiazepines, and 12% did so for antidepressants • Reasons for substitution included “less adverse side effect” (39%), “cannabis is safer” (27%), and “better symptom management” (16%)

Studies Assessing the Effect of Marijuana on Use of Prescription Drugs (continued)			
Study	Population	Methods	Outcomes
Corroon et al.[37] (2017)	• 2,774 people who used cannabis recently; respondents were from over 40 countries, but over half of respondents were from the following states: Washington, California, Oregon, or Colorado	• Online survey which collected information on substitution of cannabis for prescription drugs	• Reasons for use were not reported • 46% of patients reported using cannabis as a substitute for prescription drugs • Most common drugs substituted were opioids (36%), benzodiazepines (14%) and antidepressants (13%) • Odds of substitution was higher in medical marijuana group (60%) than non-medical marijuana group (25%)
Reiman et al.[48] (2017)	• 2,897 patients in the HelloMD digital cannabis health and wellness platform in California	• Online survey which collected information about demographics, conditions for which cannabis was used, preferred ingestion method, and use of cannabis as a substitute	• Patients reported using marijuana for pain (63%), anxiety (13%), insomnia (9%) and depression (5%) • Patients administered marijuana via smoking (50%), vaporization (31%), and edibles (10%) • 97% of patients “strongly agreed/agreed” that they were able to decrease the amount of opioids they consume when also use cannabis • 81% of patients “strongly agreed/agreed” that taking cannabis by itself was more effective at treating their condition than taking cannabis with opioids • 71% of patients “strongly agreed/agreed” that cannabis produces the same amount of pain relief as their opioid-based medications
Stith et al.[49] (2018)	• 83 patients enrolled in a New Mexico medical cannabis program (MCP) and 42 chronic pain patients who were randomly selected as a comparison group	• Prescription monitoring program records were collected and analyzed from 6 months pre-MCP enrollment to 18 months post-enrollment	• No difference in use of schedule II-IV prescriptions between two groups for 6 months pre-enrollment (average 1 Rx/month; however, at 1 year post-enrollment, 28 MCP patients and 1 comparison group patients ceased filling scheduled prescriptions altogether)

Barriers to Cannabis Use

Symptoms of Cannabis Use:[1,50]

Euphoria	Anxiety/Panic Reactions	Psychomotor Retardation	Impaired Cognition
Tachycardia	Impaired Memory	Blood Pressure Fluctuations	

Chronic cannabis uses increases the risk of:[1,7,50]

- Respiratory Dysfunction, including:
  - Chronic bronchitis
  - Impaired immunological competence leading to respiratory infections
  - Lung Cancer
- Cardiac Dysfunction, including:
  - Possible increased risk of myocardial infarction secondary to dose-related tachycardia
  - Cardiac arrhythmias
- Psychosocial Dysfunction, including:
  - Psychosis (especially schizophrenia)
  - Long-term memory impairment
  - Suicide and depression
  - Amotivational Syndrome

Cannabis Use Disorder:[1,4]

- Risk of cannabis use disorder is approximately 10% in adults and 18% in adolescents
- Classification by DSM-5[51]
  - A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two of the following within a 12-month period

1. Cannabis is often taken in larger amounts or over a longer period than was intended
2. There is a persistent desire or unsuccessful efforts to cut down or control cannabis use
3. A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects
4. Craving, or a strong desire or urge to use cannabis
5. Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home
6. Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis
7. Important social, occupational, or recreational activities are given up or reduced because of cannabis use
8. Recurrent cannabis use in situations in which it is physically hazardous
9. Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been cause or exacerbated by cannabis
10. Tolerance, as defined by either of the following: a. A need for markedly increased amounts of cannabis to achieve intoxication or desired effect b. Markedly diminished effect with continued use of the same amount of cannabis
11. Withdrawal, as manifested by either of the following: a. The characteristic withdrawal syndrome for cannabis b. Cannabis (or a closely related substance) is taken to relieve or avoid withdrawal symptoms

- Withdrawal symptoms include decreased mood and appetite and increased irritability, anxiety and depression, as well as insomnia
  - Symptoms appear with 24 hours of cessation and are most severe for the first 10 days

Cannabis and Impaired Driving:[4,50]

- Marijuana impairs driving performance and increases lane weaving
- Drivers who report using cannabis are twice as likely to report being involved in accidents than drivers who do not use cannabis
- Approximately 6-11% of fatal automobile accident victims test positive for THC (and oftentimes alcohol as well)
- Relative risk of accidents in intoxicated people who use cannabis is more modest than that of alcohol (1.3-3 vs 6-15 for alcohol)

Cannabis and Accidental Exposure:[7]

- Telephone calls to national poison control centers regarding accidental marijuana exposures have been increasing in recent years
- Acute cannabinoid toxicity in children presents as decreased coordination, decreased muscle strength, lethargy, sedation, impaired concentration, slurred speech, and slow reaction time

Cannabis and Adolescent Development:[4,52-54]

- The adolescent brain is not fully developed and is potentially susceptible to negative effects of cannabis
- Alarm has been met by reports that regular marijuana use before age 18 reduces IQ by up to 8 points by age 38, suggesting that cannabis has a neurotoxic effect on the adolescent brain
- However, a subsequent analysis of the study showed that when socioeconomic status was included as a factor, there was no effect on IQ

Conclusion

Based on Evidence:

- Although there is some clinical evidence that marijuana may be effective for neuropathic pain, there is little direct clinical data to support its efficacy as an analgesic for nociceptive pain
- Despite lack of clinical efficacy data, people who use marijuana in the community frequently due so for the treatment of a variety of pain related conditions, supporting its analgesic efficacy in the real-world setting
- Studies which assess the effect of real-world marijuana use on patient outcomes have found that:
    - Marijuana is frequently used as a substitute for prescription medications, particularly opioids
    - In states that increase access to marijuana through the approval of medical marijuana laws and dispensaries, the opioid-sparing effect of marijuana contributes to a decrease in the rate of opioid-overdose mortality, hospitalizations for opioid abuse or overdose, and detection of opioids in fatally injured drivers
- Despite the potential benefits of marijuana, its widespread use is ultimately limited by the following:
    - Safety concerns, especially regarding impairment of cognition and motor function
    - Potential for abuse and misuse
    - Complex legal status in many states

My Recommendations

- Marijuana should be reclassified as a Schedule III for the following reasons:
    - Its approval by state legislatures for a variety of conditions, including pain, contradicts the definition of a Schedule I substance which classifies drugs as having no currently accepted medical use
    - Reclassification would increase the ease and feasibility of cannabis-related research
    - Although cannabis has low-to-moderate potential for abuse and dependence, it is not dangerous and therefore does not warrant Schedule II status
    - Marijuana access can act as a harm reduction strategy in patients who use opioids for pain → fewer people die from the opioid epidemic as a result of marijuana access
    - Reclassification would enable regulation of cannabis distribution across state lines; this could improve the quality, consistency, and safety of marijuana preparations
    - Keeping marijuana as a controlled substance recognizes its potential adverse effects while allowing a safe, legal channel for people to obtain marijuana if they need it to treat a medical condition

Resources for Pharmacists

- National Institute of Health (NIH) Perspective:
    - https://www.drugabuse.gov/drugs-abuse/marijuana
- National Conference of State Legislatures (NCSL) Perspective:
    - http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx
- Professional Perspectives:
    - Lawrence Leung. Cannabis and its Derivatives: Review of Medical Use. J Am Board Fam Med. 2011; 24;452-62.
    - Seddon Savage, et al. Cannabis in Pain Treatment: Clinical and Research Considerations. J Pain. 2016;17:654-68

References

1. Leung L. Cannabis and its derivatives: review of medical use. J Am Board Fam Med 2011;24:452-62.
2. Marijuana. National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services., 2017. (Accessed January 5, 2018, at https://www.drugabuse.gov/publications/drugfacts/marijuana.)
3. Marijuana and Public Health. Centers for Disease Control and Prevention, 2017. (Accessed January 5, 2018, at https://www.cdc.gov/marijuana/index.htm.)
4. Doering PL, Li RM. Substance-Related Disorders I: Overview and Depressants, Stimulants, and Hallucinogens. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach, 10e. New York, NY: McGraw-Hill Education; 2017.
5. Marijuana as Medicine. National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services., 2017. (Accessed January 5, 2018, at https://www.drugabuse.gov/publications/drugfacts/marijuana-medicine.)
6. Kendall DA, Yudowski GA. Cannabinoid Receptors in the Central Nervous System: Their Signaling and Roles in Disease. Front Cell Neurosci 2016;10:294.
7. Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. Pharmacotherapy 2013;33:195-209.
8. Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: Its relevance to rheumatic disease. Eur J Rheumatol 2017;4:210-8.
9. Araque A, Castillo PE, Manzoni OJ, Tonini R. Synaptic functions of endocannabinoid signaling in health and disease. Neuropharmacology 2017;124:13-24.
10. Fonseca BM, Costa MA, Almada M, Correia-da-Silva G, Teixeira NA. Endogenous cannabinoids revisited: a biochemistry perspective. Prostaglandins Other Lipid Mediat 2013;102-103:13-30.
11. Temple LM. Medical marijuana and pain management. Dis Mon 2016;62:346-52.
12. Hazekamp A, Ware MA, Muller-Vahl KR, Abrams D, Grotenhermen F. The medicinal use of cannabis and cannabinoids--an international cross-sectional survey on administration forms. J Psychoactive Drugs 2013;45:199-210.
13. Savage SR, Romero-Sandoval A, Schatman M, et al. Cannabis in Pain Treatment: Clinical and Research Considerations. J Pain 2016;17:654-68.
14. Romero-Sandoval EA, Kolano AL, Alvarado-Vazquez PA. Cannabis and Cannabinoids for Chronic Pain. Curr Rheumatol Rep 2017;19:67.
15. Pacula RL, Jacobson M, Maksabedian EJ. In the weeds: a baseline view of cannabis use among legalizing states and their neighbours. Addiction 2016;111:973-80.
16. Sate Medical Mairjuana Laws. National Conference of State Legislatures, 2018. (Accessed January 28, 2018, at http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx.)
17. 29 Legal Medical Marijuana States and DC. 2017. (Accessed January 14, 2018, at https://medicalmarijuana.procon.org/view.resource.php?resourceID=000881.)
18. Ryan-Ibarra S, Induni M, Ewing D. Prevalence of medical marijuana use in California, 2012. Drug Alcohol Rev 2015;34:141-6.
19. Walsh Z, Callaway R, Belle-Isle L, et al. Cannabis for therapeutic purposes: patient characteristics, access, and reasons for use. Int J Drug Policy 2013;24:511-6.
20. Reinarman C, Nunberg H, Lanthier F, Heddleston T. Who are medical marijuana patients? Population characteristics from nine California assessment clinics. J Psychoactive Drugs 2011;43:128-35.
21. Medical Marijuana Patient Numbers. Marijuana Policy Project, 2018. (Accessed February 13, 2018, at https://www.mpp.org/issues/medical-marijuana/state-by-state-medical-marijuana-laws/medical-marijuana-patient-numbers/.)
22. Kalata J. Medical Uses of Marijuana: Opinions of U.S. Residents 45+. AARP the Magazine: AARP; 2004.
23. Stanos S, Brodsky M, Argoff C, et al. Rethinking chronic pain in a primary care setting. Postgrad Med 2016;128:502-15.
24. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007;68:515-21.
25. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008;9:506-21.
26. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009;34:672-80.
27. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010;182:E694-701.

28. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013;14:136-48.
29. Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A. An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabis in the Treatment of Neuropathic Pain From Spinal Cord Injury and Disease. J Pain 2016;17:982-1000.
30. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. J Pain 2015;16:616-27.
31. Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. CMAJ 2012;184:1143-50.
32. Opioid Overdose. Centers for Disease Control and Prevention, 2017. (Accessed January 5, 2018, at https://www.cdc.gov/drugoverdose/.)
33. Katz J. You Draw It: Just How Bad Is the Drug Overdose Epidemic? The New York Times 2017 October 26.
34. The U.S. Opioid Epidemic. U.S. Department of Health and Human Services, 2017. (Accessed January 5, 2018, at https://www.hhs.gov/opioids/about-the-epidemic/index.html.)
35. Leading Causes of Death. CDC/National Center for Health Statistics, 2017. (Accessed January 5, 2018, at https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm.)
36. Relieving Pain in America: A Blueprint on Advancing Pain Research, Care, and Education and Research. Washington, D.C.: The National Academies Press; 2011.
37. Corroon JM, Jr., Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs - a cross-sectional study. J Pain Res 2017;10:989-98.
38. Opioid Overdose Crisis. National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services., 2018. (Accessed January 5, 2018, at https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis.)
39. Reisfield GM, Wasan AD, Jamison RN. The prevalence and significance of cannabis use in patients prescribed chronic opioid therapy: a review of the extant literature. Pain Med 2009;10:1434-41.
40. Cerda M, Wall M, Keyes KM, Galea S, Hasin D. Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. Drug Alcohol Depend 2012;120:22-7.
41. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Intern Med 2014;174:1668-73.
42. Hayes MJ, Brown MS. Legalization of medical marijuana and incidence of opioid mortality. JAMA Intern Med 2014;174:1673-4.
43. Powell DP, R.L.; Jacobson, M. Do Medical Marijuana Laws Reduce Addictions and Deaths Related to Pain Killers? NBER Working Paper Series2015.
44. Shi Y. Medical marijuana policies and hospitalizations related to marijuana and opioid pain reliever. Drug Alcohol Depend 2017;173:144-50.
45. Kral AH, Wenger L, Novak SP, et al. Is cannabis use associated with less opioid use among people who inject drugs? Drug Alcohol Depend 2015;153:236-41.
46. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. J Pain 2016;17:739-44.
47. Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. Int J Drug Policy 2017;42:30-5.
48. Reiman A, Welty M, Solomon P. Cannabis as a Substitute for Opioid-Based Pain Medication: Patient Self-Report. Cannabis Cannabinoid Res 2017;2:160-6.
49. Stith SS, Vigil JM, Adams IM, Reeve AP. Effects of Legal Access to Cannabis on Scheduled II-V Drug Prescriptions. J Am Med Dir Assoc 2018;19:59-64 e1.
50. Hall W. The adverse health effects of cannabis use: what are they, and what are their implications for policy? Int J Drug Policy 2009;20:458-66.
51. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.
52. Jensen B, Chen J, Furnish T, Wallace M. Medical Marijuana and Chronic Pain: a Review of Basic Science and Clinical Evidence. Curr Pain Headache Rep 2015;19:50.
53. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A 2012;109:E2657-64.
54. Rogeberg O. Correlations between cannabis use and IQ change in the Dunedin cohort are consistent with confounding from socioeconomic status. Proc Natl Acad Sci U S A 2013;110:4251-4.