Medical Marijuana

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MMDA
Chicago, IL
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Learning Objectives

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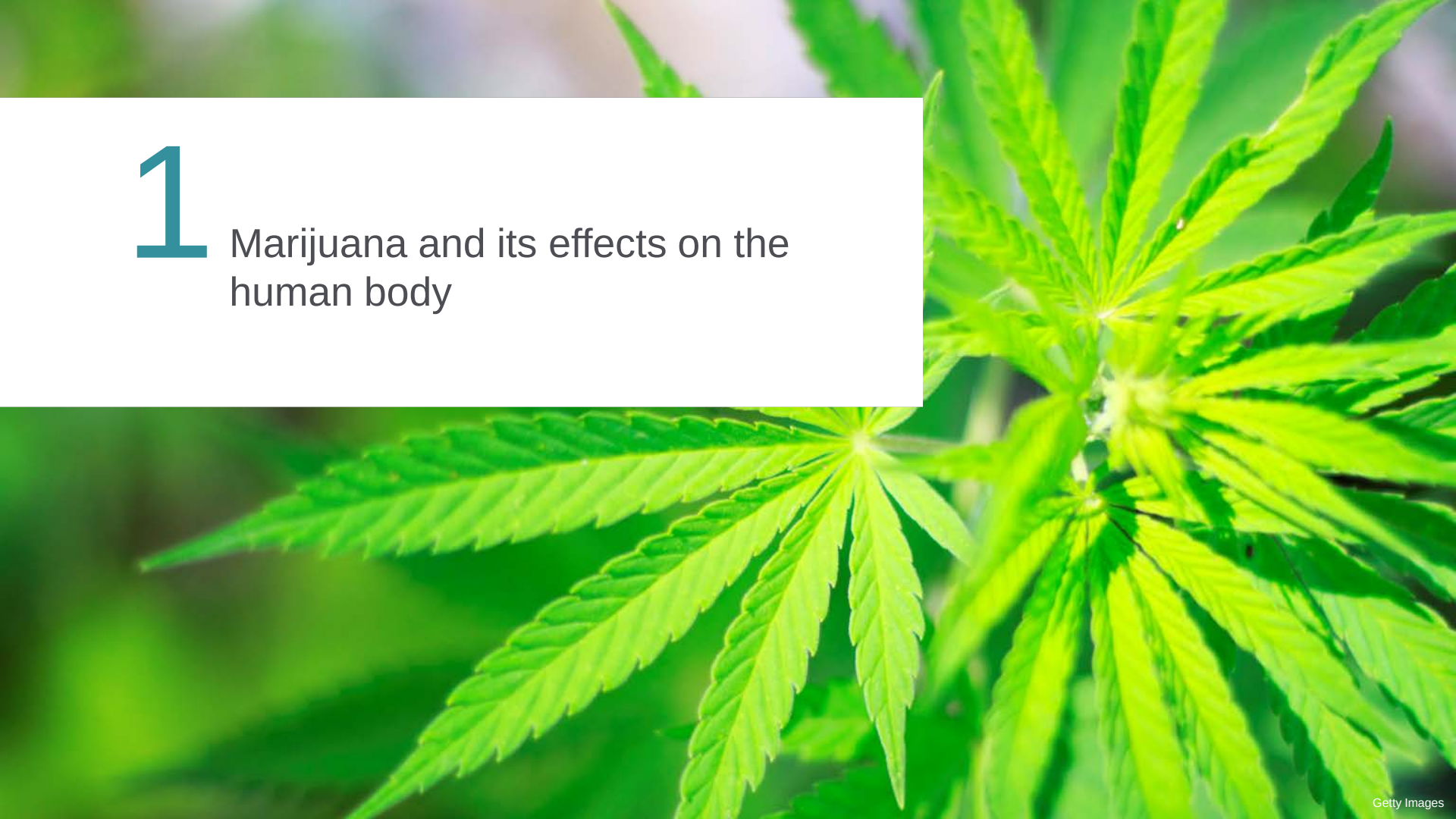
1. Provide an **introduction** to marijuana and its effects on the human body
2. Discuss the **history** of medical marijuana in the USA
3. Discuss the **“marijuana revolution”** currently occurring in the USA
4. Discuss current **clinical evidence** for use of medical marijuana
5. Discuss **implications** for the physician and the insurance industry

1 Marijuana and its effects on the human body



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Marijuana = Cannabis

- Generic term for any drugs/chemicals derived from plants genus *Cannabis*
- Typically the dried leaves and flowering tops of *Cannabis sativa*
- Most commonly used illicit drug worldwide
- Ability to alter sensory perception and cause elation and euphoria (the “high”)
- Hundreds of various strains and hybrids
- Active compounds are called **cannabinoids**
  - 70+ identified so far
  - Primary cannabinoids in marijuana
    - THC = delta-9-tetrahydrocannabinol - most psychoactive
    - CBD = cannabidiol - not psychoactive, may mitigate effects of THC

Cannabinoid Receptor System
(discovered in 1990)

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- Endogenous anandamine discovered in 1992
- Endocannabinoid system is transiently activated under certain stressful conditions to restore homeostasis

CB1 receptor	CB2 receptor
Brain and spinal cord (primarily) Peripheral nerves Muscle, liver, adipose tissue	Mainly on cells of the immune system (spleen, WBCs, tonsils)
Inhibits release of several neurotransmitters (acetylcholine, L-glytamate, GABA, norepinephrine, dopamine)	Regulates immune responses and inflammatory reactions (cytokine release)
Psychoactive effects – areas that affect pleasure, memory, pain, thinking, concentration, coordination	No psychoactive effects Anti-inflammatory Anti-cancer
Binding site for THC	Binding site for CBD

Overall Health Effects of Marijuana

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- Related mostly to THC content and its interaction with CB1 receptor
- Potency determined by THC content
  - THC level
  - THC/CBD ratio
  - CBD may mitigate effects of THC
- Many strains and hybrids have been “engineered” to achieve desired effects
- Limited number of CB1 receptors in the brain stem

Overall Health Effects of Marijuana

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- Central Nervous System
  - Memory loss, learning disability
  - Depression, paranoia, addiction
  - Anxiety
- Cardiovascular system
  - Increased blood pressure and heart rate
  - Increased risk for heart attack
- Digestive system
  - Acute hunger (“munchies”)
  - Constipation
- Respiratory (when smoked)
  - Bronchitis
  - Lung cancer

Herbal Form of Marijuana

- Dried leaves and flowering tops
- Majority of users smoke or inhale
  - 50% of cannabinoid THC is inhaled in the smoke
  - Rapid absorption of almost all THC into blood stream to brain
  - Effects noticeable within minutes
- Contains > 400 different chemicals
- 4 times the level of tar in a marijuana cigarette (vs. tobacco)

Multiple varieties/strains of smoked marijuana

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- Cannabis plants vary in smell, color, growth rate, bud size, therapeutic and medicinal effect
- 700+ varieties have been identified

Variety	THC	CBD	Type
Bedrocan	19	-	sativa
Bedrobinol	12	-	sativa
Bediol	6	7.5	sativa
Bedica	14	-	indica

(contents are indicated as % of dry weight; in other words 1% is equivalent to 10 mg present per 1 gram of dry weight cannabis)

Cannabidiol (CBD)

- Binds to CB2 receptor, found mainly in body's immune system
- Little to no effect on CB1 receptors with very low affinity (100 fold less than THC)
- Does not produce euphoria or intoxication (unlike THC)
- Preclinical research (cell-culture, animal models) shows promise as:
  - **Anti-seizure**, neuroprotective, anti-psychotic, anti-anxiety
  - Anti-oxidant
  - Anti-inflammatory
  - Analgesic
  - Anti-tumor
- CBD oil, high-CBD strains of marijuana

2 History of Medical Marijuana (USA)

History of Medical Marijuana

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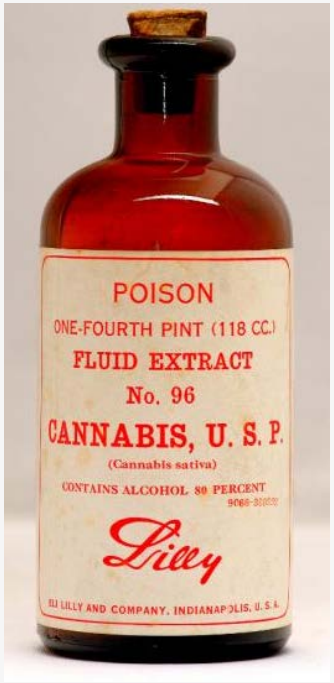
gout
rheumatism
malaria
poor memory

seizures
nausea
menstrual
cramps

headache, muscle spasm, menstrual cramps, rheumatism, convulsions of tetanus, childbirth pain, sleep sedative, depression, opium withdrawal

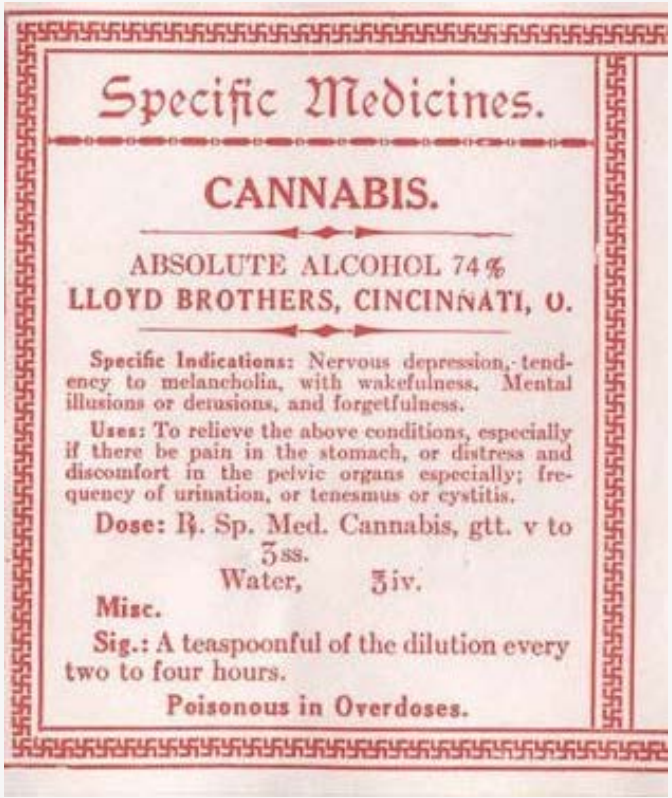
Pure Food and Drug Act of 1906

- Consumer protection act to combat “poisonous” foods, drugs, medicines, liquors
- Introduced proper labeling



www.cnn.com The quick hit history of medical marijuana

Indications Medical Marijuana



Specific Medicines.

CANNABIS.

ABSOLUTE ALCOHOL 74%
LLOYD BROTHERS, CINCINNATI, O.

Specific Indications: Nervous depression, tendency to melancholia, with wakefulness. Mental illusions or delusions, and forgetfulness.

Uses: To relieve the above conditions, especially if there be pain in the stomach, or distress and discomfort in the pelvic organs especially; frequency of urination, or tenesmus or cystitis.

Dose: ℞. Sp. Med. Cannabis, gtt. v to ʒss.
Water, ʒiv.
Misc.

Sig.: A teaspoonful of the dilution every two to four hours.

Poisonous in Overdoses.

Nervous depression
Tendency to melancholia
Mental illusions or delusions
Forgetfulness

Marijuana Tax Act of 1937

- Made possession and transfer of cannabis illegal in the USA
- Imposed an occupational excise tax upon certain dealers in marijuana and added transfer tax
- If you wanted to buy marijuana, you needed a stamp

The Four Perforate Stamps of the historic first issue (MA732)

$100 stamp comes with attached Receipt Tab

Controlled Substances Act of 1970

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- Comprehensive Drug Abuse Prevention and Control Act
- Combat and control drug abuse and dependence
- Developed five categories based on abuse potential and clinical usefulness
- **Schedule 1 drugs**
  - **No accepted medical use**
  - **High potential for abuse**
  - **Lack accepted safety data**
  - Cannot be prescribed by physicians
  - Heroin, LSD, **marijuana**

Current Status of Medical Marijuana in the USA

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- Schedule 1 drug (no accepted medical use, high potential for abuse)
- Confirmed 2001 and 2006
- Only two FDA-approved* cannabinoid drugs
  - dronabinol, nabilone – synthetic THC capsules
  - Limited indications (N/V chemotherapy, anorexia AIDS)
  - Not widely used (effectiveness)
- No FDA-approved medications that are smoked

* FDA = Food and Drug Administration (responsible for approval/marketing of drugs in the USA)

FDA-approved cannabinoid drugs (USA)*

(compounds structurally similar to marijuana)

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Drug name	Forms	Indications	FDA approval
dronabinol (Marinol)	synthetic version of THC capsules	nausea and vomiting due to cancer chemotherapy anorexia associated with weight loss in AIDS	5/31/85 12/22/92 Schedule III drug
nabilone (Cesamet in US; Canemes, in Austria; UK, Mexico)	synthetic cannabinoid CB1 receptor 1 mg capsule	nausea and vomiting due to cancer chemotherapy (second line therapy)	12/26/85 (but never marketed in the US until May 2006) Schedule II Drug of Controlled Substance Act (high potential for abuse)

*currently NO FDA-approved medications that are smoked; oral versions not widely used(effectiveness)

Investigational drugs currently undergoing FDA trials

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Drug name	Forms	Indications	Approval status
delta-9-tetrahydrocannabinol and canabidiol (Sativex®)	cannabis extracts from *Cannabis sativa* (leaf/flower) 2.7 mg THC + 2.5 mg CBD per 100 microliter spray oromucosal spray	Spasticity due to Multiple Sclerosis (MS) Neuropathic Pain (in MS) Moderate/Severe Pain in advanced cancer	Approved in 18 European countries + New Zealand Israel Canada Canada FDA - Phase 3 Clinical Trials in USA
cannabidiol (Epidiolex©)	syrup/oil 99% CBD (almost no THC)	Dravet syndrome – rare intractable childhood epilepsy	Very favorable initial results FDA Fast Track approval (pending)

3 The Marijuana Revolution

Getty Images

Medical Marijuana

- 1996 – California – Proposition 215 – The Compassionate Use Act of 1996
  - Approved for use by “seriously ill” individuals with MD recommendation
- 2009 – US Attorney General – relaxed federal law enforcement
    - Rapid rise in medical marijuana licenses
    - Colorado: 4819 (12/08) => 116,000 (9/14)
- 2013 – US Department of Justice – advised US attorneys not to pursue action against physicians
- 2016 – medicinal marijuana legalized in 40 states
  - 23 states, DC, Guam – comprehensive public programs
  - 17 additional states – allow low THC (0.8%, 3%. 5%) products for limited situations
- Rationale – compassionate care; increase quality of life

Recreational Marijuana

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- Nov 2012 – Colorado – Amendment 64 – legalized recreational marijuana
- Jan 2014 – Colorado retail stores opened for business
  - Cash business, some shops > 500 customers/day
  - $53 million in tax revenue in first year (28% tax rate)
- Feb 2016 – recreational marijuana legalized in 4 states
  - Colorado (2012), Washington (2012), Alaska (2014), and Oregon (2014)
- No public consumption, cannot transfer out-of-state
- Several additional states have “decriminalized” marijuana

Marijuana Laws in the USA by State

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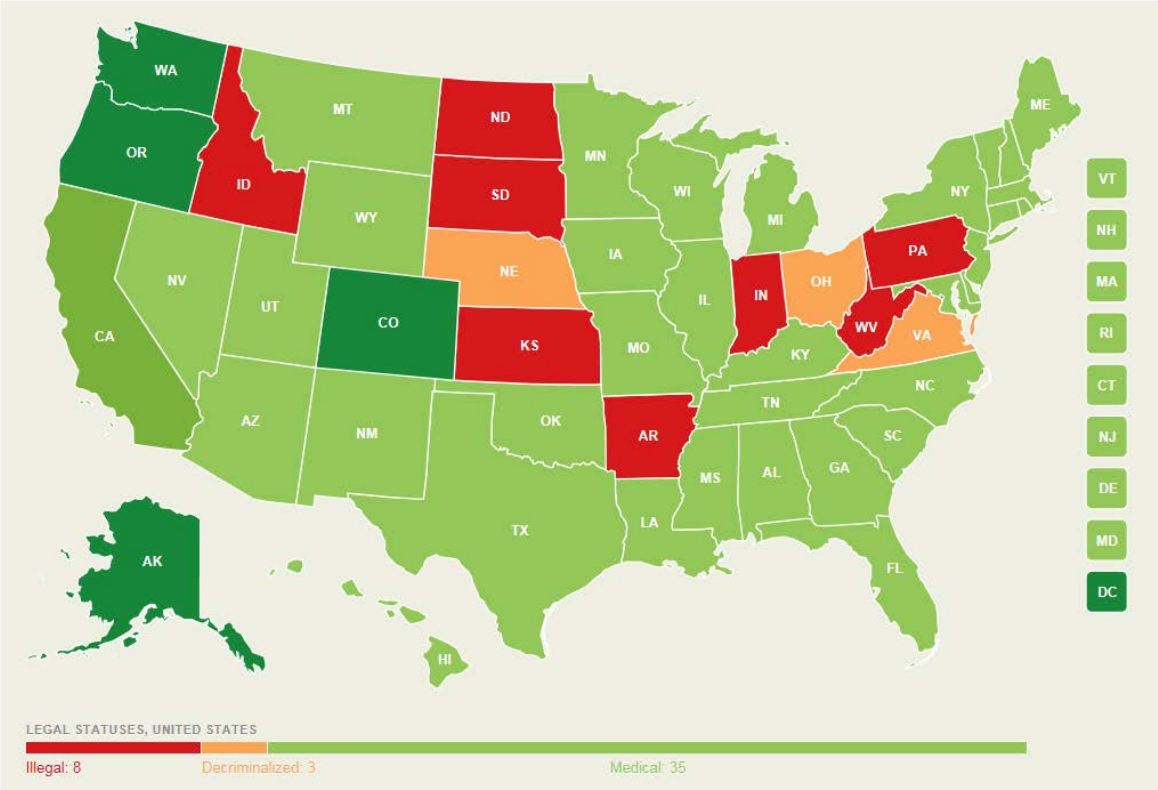

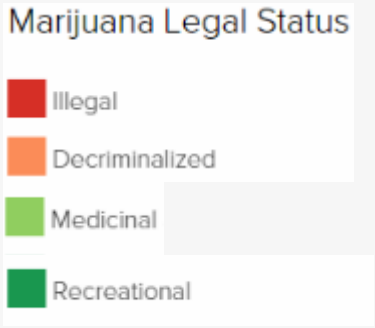

www.leafly.com (February 1, 2016)

Patient Access to Medical Marijuana

While each state has their own specific procedures, in general, this is the process:

1. Visit a physician
2. Obtain physician certification
   - Qualified condition that may benefit from medical marijuana
   - History and Physical
   - Informed consent (risk/benefit ratio)
3. Medical marijuana obtained (dispensary or treatment center)

Physician cannot legally “prescribe” medical marijuana only “certify” potential benefit

Not available from pharmacies because it’s federally illegal

Ann Med 2016 Feb 25:1-14

4 Medical Marijuana – clinical evidence

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- Use of marijuana or “marijuana-like” compounds for medicinal purposes
- Efficacy related to cannabinoid involved and receptor interaction (CB1, CB2)
- Includes forms other than smoked herbal marijuana
- “Medical marijuana” can include:
  - Herbal marijuana that is smoked, vaporized, or ingested with variable THC/CBD content
  - Synthetic analogues that mimic THC (e.g. dronabinol, nabilone)
  - THC capsules
  - THC oil
  - Nabiximols oromucosal spray (THC/CBD)
  - CBD only pills

Medical Marijuana

(What are the efficacy and safety of cannabinoids used for various medical conditions?)

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Original Investigation

Cannabinoids for Medical Use

A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

IMPORTANCE Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear.

OBJECTIVE To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids.

DATA SOURCES Twenty-eight databases from inception to April 2015.

STUDY SELECTION Randomized clinical trials of cannabinoids for the following indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette syndrome.

28 databases
79 RCTs (23,754 screened)
6462 participants

4 low risk of bias
55 high risk of bias
(incomplete outcome data, inadequate blinding, no statistical significance)

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358.

Medical Marijuana

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- Improvement in symptoms, but not statistically significant
- Poor quality data
- Moderate quality evidence to suggest benefit
  - Chronic neuropathic or cancer pain
  - Spasticity due to MS
- Reduce nausea and vomited due to chemotherapy (low-quality evidence)
- Limited evidence to support cannabinoids for other medical conditions
- Primarily considered oral cannabinoids and not other routes (e.g. inhaled or ingested)
- No assessment of long-term side effects

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358.

Medical Marijuana

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No evidence of benefit

- Depression
- Anxiety
- Psychosis
- Hepatitis C
- Crohn disease
- Parkinson disease
- Glaucoma

Increase side effects

- Dizziness
- Nausea and vomiting
- Sleepiness
- Disorientation
- Confusion
- Hallucinations

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358.

Qualifying Conditions (by state law)

- Most medical conditions not supported by solid clinical research
- No consistency in the USA
- Wide variability in “approved” conditions (based on low-quality evidence, anecdotal reports, public opinion, advisory board or council)
- Criteria very broad in some states
  - Any “serious medical condition” for which medical use of marijuana (cannabis) is “appropriate”
  - “Chronic Pain”
    - Chronic fibromyalgia
    - Migraine headaches
    - Arthritis

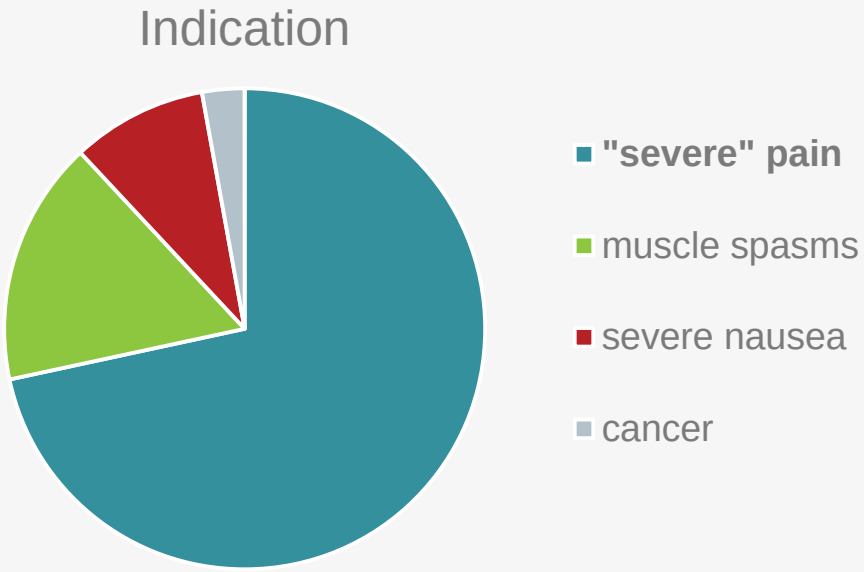
Anecdotal Case Reports – Newspaper Headlines

Intractable Seizure Disorder

- 4-year-old girl with intractable epilepsy; >100 visible seizures a day
- Moved from Ohio to Colorado for Medical Marijuana
- Medical marijuana – THC patches and oil (orally)
- Dramatic shift in demeanor (from lethargic/withdrawn to vibrant and playful)

Qualifying Conditions – Colorado

Colorado Medical Marijuana Registry

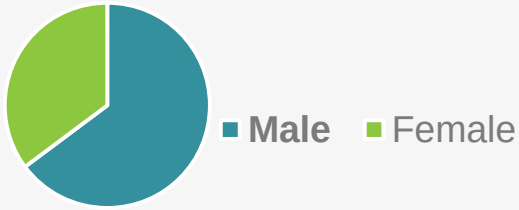


www.colorado.gov/cdphe/medicalmarijuana

January 31, 2016

320,229 patients
107,798 active patients

13.3% have dedicated PCP
232 different physicians



average age 42.5

Chronic Pain

- 28 studies (2454 patients)
- Only 4 were for smoked THC
  - 1-5 cigs/day (2.5% to 9.4%) vs. placebo
- Conditions
  - Neuropathic Pain
  - Cancer Pain
  - HIV-associated sensory neuropathy
  - Refractory pain due to MS or other neurological conditions
  - Chemotherapy-induced pain
- Research supports compassionate care; increase quality of life

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358.

Risk for Drug Abuse

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- Is nearly all “medical” marijuana use in the USA actually disguised recreational use?
  - Most current users were already regular marijuana users
  - 91% use for “pain”
- 33% increase frequency of use in teens (high risk group)
  - medical marijuana states vs 6% for the rest of the country
- 24.8% lower mean annual opioid mortality rate
  - “direct causal link cannot be established”
- “Medical marijuana got me off narcotic pain pills” - anecdotal case report
  - 100 Percocet pills/month => 1 joint three times/day (AZ)
  - Ex-Chicago Bear, Jim McMahon

Journal of Global Drug Policy and Practice (2014), National Survey on Drug Abuse and Health
JAMA Internal Medicine. Aug 25, 2014, Chicago Tribune, Jan 29, 2016

Medical Marijuana User Demographics

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Survey	San Francisco Bay Area	Los Angeles county	Illinois
	N = 4117	N = 1746	N = 3300
Date	2001-2007	2006	2015
Sex	Male (77%)	Male (72.9%)	Female (60%)
Average Age	32 years old	25-34 y/o (> 55/y/o only 13%)	>51 y/o (> 50%)
Prior regular cannabis use < 19 y/o	YES – 89%	YES – 67%	
Amount and frequency of use	Daily regular user 1/8 to ¼ ounce/week	Daily regular user	
Qualifying condition	Not assessed	Pain, insomnia, anxiety	Severe fibromyalgia, cancer, spinal cord
	O'Connell, Harm Reduct J. 2007	J Psychoactive Drugs. 2011;43(2)	IL Dept of Public Health

Medical Marijuana Users – California

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Los Angeles county

Focus groups (N=30), survey of dispensary users (N=182)

- Most had initiated marijuana use in adolescence
- 50% had indications of risky alcohol use
- 20% admitted use of illicit drugs or misuse of prescription medications
- Higher risk in the younger < 30 years old age group
  - Higher rates of tobacco use
  - Visited dispensaries more frequently
- 65% reported “psychological distress” within the past year
- Nearly all believed medical marijuana was beneficial for the health problems

J Psychoactive Drugs. 2014 Oct-Dec;46(4):267-75.

Medical Marijuana Users – California vs. Netherlands

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	California	Netherlands
Recreational Marijuana	Illegal	1970s (decriminalized)
Medical Marijuana (legalized date)	1996	2003
Date	2005-2010	2005-2010
Annual rates of use	7000 per 100,000	8 -10 per 100,000
Sex	Male (77%)	Male (72.9%)
Average Age	40.7 years	55.6 years
Prior regular cannabis use < 19 y/o	YES – 89%	YES – 67%
Average daily dose	2.4-3.8 grams	0.68 grams
Indications	Pain, insomnia, anxiety	Chronic pain

Hazekamp A, Eur J Clin Pharmacol. 2013;69(8):1575-80

5 Implications for the Physician and the Insurance Industry

Getty Images

Implications for the Physician in the USA

- Limited medical evidence to support majority of “qualifying” conditions
- No clear “best practices” (amount, variety, dosing regimen) esp. for smoked marijuana
  - Dosing strategy = “start slow, titrate up”
- Lack of knowledge and comfort level to prescribe
- Ethical dilemma between compassionate care and adverse outcomes
- Risk for arrest and federal prosecution as well as malpractice risk
- Long term risks remain unclear (psychotic disorder, cognitive impairment, drug tolerance, drug dependency)

No clear dosing strategy

- Start slow – titrate up!
- THC content varies
- Must include name, amount, variety, and dosing regimen
- Examples:
  - Amount (FIVE grams)
  - 200 ml tea (prepared from 1 gram cannabis per 1 L of water) – increase dose/volume or frequency as tolerated
  - 100-200 mg use of high quality vaporizer, max 3dd.

Edible Varieties

Edible Varieties – Risk for Overdose

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- Estimated 16-26% of medical marijuana users consume edible products
  - Lacks harmful by-products of smoking
  - Delayed effects (peak 30 min – 3 hours; duration 12 hours)
  - Less bioavailability than when smoked
- Manufacturing of edible products is not standardized in the USA
- Risk for unintentional overdose, intoxication, and death
  - One cookie (100 mg THC), one brownie (200 mg THC); overdose possible with 10-30 mg THC
  - Death – Colorado – 19 years old – after ingesting one cookie (March 2014)
  - Higher risk in children
    - appealing packaging (cookie, candy), not childproof
    - “Children’s Hospital of Colorado – increase in unintentional marijuana ingestion

Edible Varieties – Labeling is Poor

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- Manufacturing NOT Standardized

- 75 edible marijuana products (47 different brands) – San Francisco, Los Angeles, Seattle
  - **Only 17% were labeled correctly**
  - 60% at least 10% LOWER (some with negligible amounts!)
  - 23% at least 10% HIGHER
  - Study random 3 each city (SF,CA, LA,CA, Seattle) dispensaries with at least 1 product in each of 3 categories (baked goods, beverages, candy/chocolate) with labeled specific THC content
- Aug – Oct 2014, $400/city

JAMA June 23/30, 2015 Volume 313, Number 24

Pharmacokinetics

	Smoked marijuana	Edible varieties of marijuana
Clinical effect	5 min	30 min
Peak	30-90 min	3 hours
Duration	4 hours	12 hours

Clin Pharmacokinet. 2003;42(4):327-360

Marijuana and “Drugged” driving

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- Fatal car crashes involving marijuana have TRIPLED in the USA (1999-2010)
  - California
    - More than 40% increase in drivers killed in crashes who tested positive for drugs (2009-2013)
    - Marijuana-related fatal accidents EQUAL to Alcohol-related fatal accidents (BAC ≥ 0.08% legal limit) (Los Angeles and San Francisco)
    - Increase in marijuana-related admissions to emergency rooms
  - Colorado
    - 32% increase in marijuana-related traffic deaths (year after 2013 recreational use law)

Am J Epidemiology

Cigarette, Cigar, and Marijuana Use Among High School Students – United States, 1997-2013

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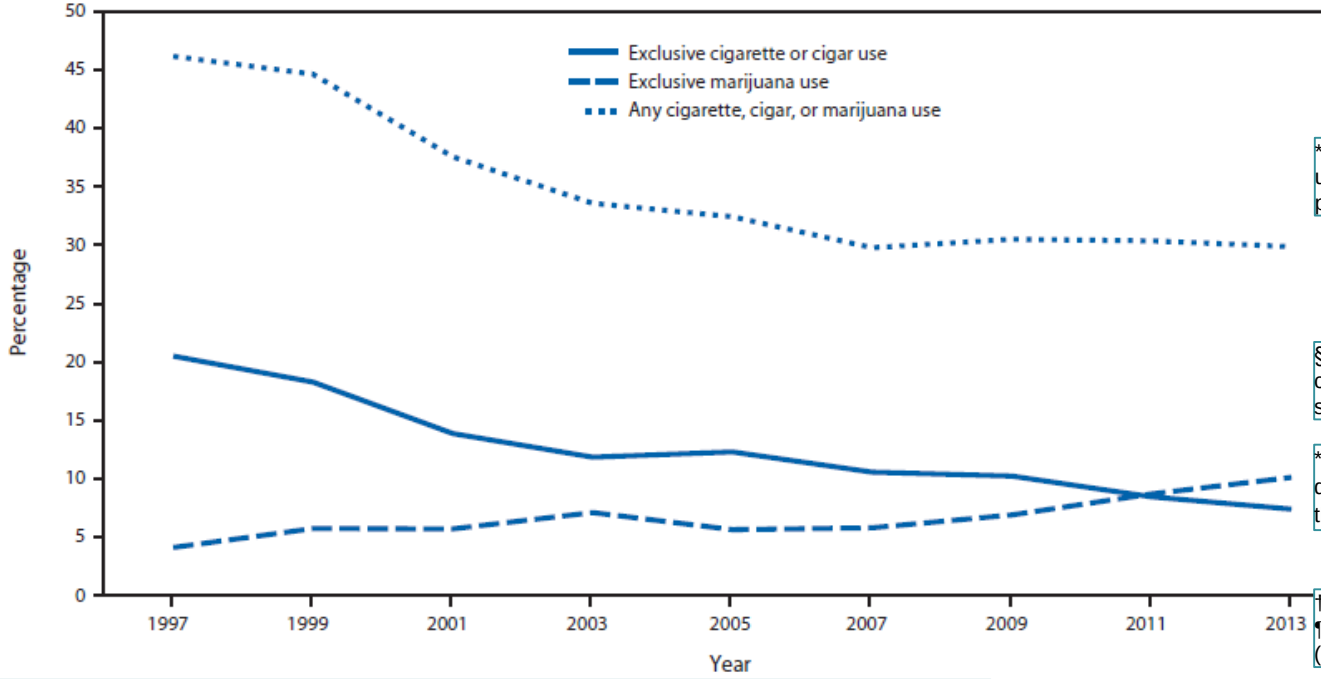
FIGURE 1. Prevalence of exclusive cigarette or cigar use,*† exclusive marijuana use,†§ and any cigarette, cigar, or marijuana use†¶ among high school students†† during the 30 days preceding the surveys — National Youth Risk Behavior Surveys, United States, 1997–2013**



** Used cigarettes or cigars on one or more days, or used marijuana one or more times during the 30 days preceding the survey.

§ Used marijuana one or more times, but did not use cigarettes or cigars during the 30 days preceding the survey.

* Used cigarettes or cigars on one or more days, but did not use marijuana during the 30 days preceding the survey.

† Significant linear trend during 1997–2013 (p<0.01).
¶ Significant quadratic trend during 1997–2013 (p<0.01).

†† Students with missing data for cigarette use, cigar use, marijuana use, or sex and students who did not self-identify as non-Hispanic black, non-Hispanic white, or Hispanic were excluded from the analysis.

www.cdc.gov

Marijuana and Dependency

- Tobacco (30%)
- Heroin (25%)
- Cocaine (20%)
- Alcohol (14%)
- Marijuana (9%)
  - Higher for those beginning use in adolescence

National Institute on Drug Abuse

Implications for the Insurance Industry

- Mortality/Morbidity
  - Long term risks remain unclear
    - psychosis/psychiatric impairment
    - cognitive impairment
    - drug tolerance and drug dependence
  - Increase in “drugged” driving and accidents
  - Risk for abuse – substitute for narcotics or alcohol
- Health
  - Increase in health care utilization (emergency rooms, poison control)

Medical Marijuana and Insurability

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- Evaluate underlying disease; possibly already uninsurable
- Age
- Type of marijuana, amount, and frequency
- Comorbid impairments
  - psychiatric disease (depression, etc)
  - alcohol or other substance abuse
  - lung or cardiovascular disease
- Smoker vs. Non-smoker rates
  - Informal 2014 Munich Re survey - 29% life insurers classify as nonsmokers

Medical Marijuana – Take Home Messages

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- “Medical Marijuana” is not going away
- Includes forms other than smoked herbal marijuana
- Ongoing legalization/decriminalization of recreational marijuana only complicates the picture
- Not first-line therapy for any medical condition
- Proven therapeutic benefit for chronic neuropathic or cancer pain and spasticity due to MS
- Clinical research lacking for most “approved” conditions with limited studies on smoked marijuana
- Rapidly evolving landscape
- More research is required
- Impact of cannabidiol (CBD) research could be huge

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“Having access to a drug or medical treatment, without knowing how to use it or even if it is effective, does not benefit anyone. Simply having access, without having safety, efficacy, and adequate use information does not help patients.”

Robert J Meyer, MD, Director, Office of Drug Evaluation (FDA, US Dept Health and Human Services, April 2004) www.fda.gov

Thank you very much for your attention!

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