ScottCare Spring Forward Conference

Cannabis and the Heart – Considerations for the Rehab Setting

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February 2021

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab
COURAGE LIVES HERE
Cardiovascular Prevention and Rehabilitation

UNIVERSITY OF TORONTO FACULTY OF MEDICINE

Peter Munk Cardiac Centre UHN

Outline

At the end of this session, the participant will be able to:

- Describe the pharmacology of cannabis and the different effects of THC and CBD
- Be aware of the adverse effects of cannabis (THC) on the cardiovascular system
- Update on the particular risk of vaping and lung injury
- Anticipate potential drug interactions
- Bonus item: Have insight into choosing a "*kush*" vs. "*sativa*"

Cannabis Stories

- 65 yo woman with known CAD – occasional cannabis smoker – any CV concerns?
- 35 yo man with acute coronary syndrome; frequent cannabis smoker – any relationship?
- 75 yo man – admitted to hosp with delirium and tachycardia – is this cannabis related??
- 70 yo woman – post CABG + AVR – is CBD ok?

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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THE PRESENT AND FUTURE

JACC REVIEW TOPIC OF THE WEEK

Marijuana Use in Patients With Cardiovascular Disease

JACC Review Topic of the Week

Ersilia M. DeFilippis, MD,[a] Navkaranbir S. Bajaj, MD, MPH,[b] Amitoj Singh, MD,[c] Rhynn Malloy, PharmD,[d] Michael M. Givertz, MD,[d] Ron Blankstein, MD,[d] Deepak L. Bhatt, MD, MPH,[d] Muthiah Vaduganathan, MD, MPH[d]

DeFilippis, E.M. et al. J Am Coll Cardiol. 2020;75(3):320–32.

Journal of Clinical Medicine

Latif and Garg. J. Clin. Med. **2020**, *9*, 1925;
doi:10.3390/jcm9061925

MDPI

Review

The Impact of Marijuana on the Cardiovascular System: A Review of the Most Common Cardiovascular Events Associated with Marijuana Use

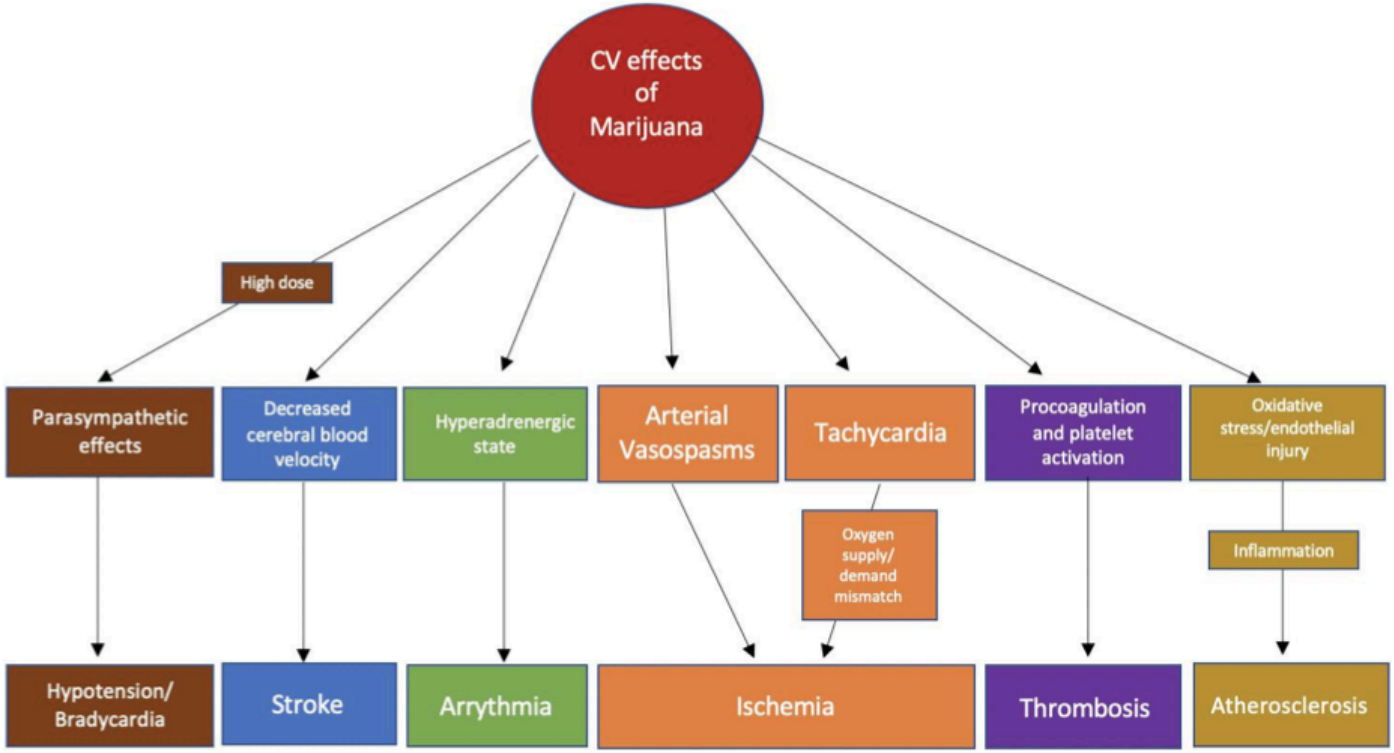


Figure 1. Possible pathophysiological mechanisms of the association of common cardiovascular events with marijuana use.

Circulation

Circulation. 2020;142:e131–e152.
Sept 8 2020

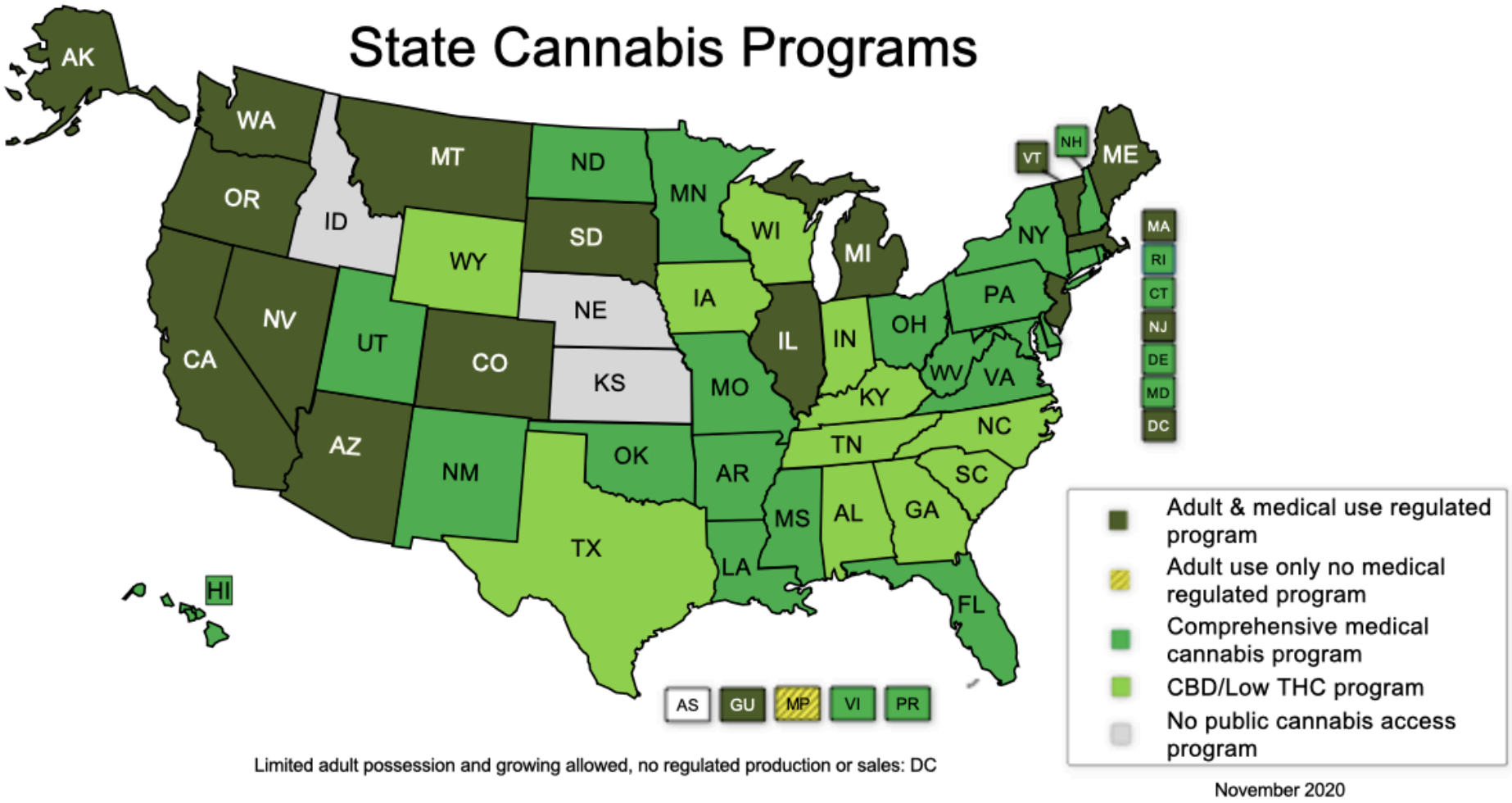
AHA SCIENTIFIC STATEMENT

Medical Marijuana, Recreational Cannabis, and Cardiovascular Health

A Scientific Statement From the American Heart Association

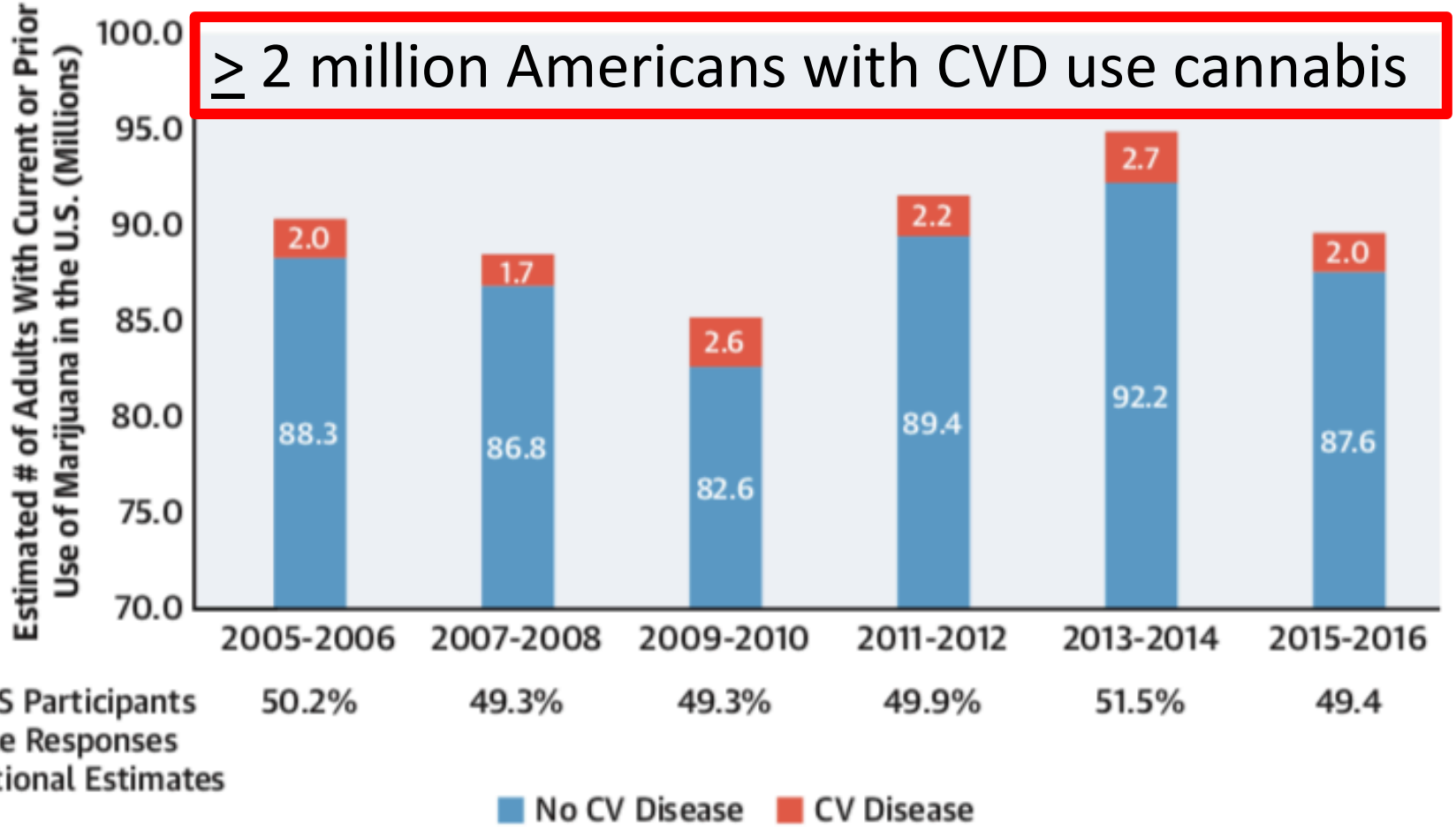
- Epidemiology
- Pharmacology – formulations, dosing, metabolism
- Clinical benefits
- Safety and adverse effects
- Summary of studies
- Considerations in special populations

Evolving Policy Landscape



https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

FIGURE 3 Estimated 1.7 to 2.7 Million Adults Reporting Prior or Current Marijuana Use Who Have Cardiovascular Disease, 2005 to 2016, From NHANES



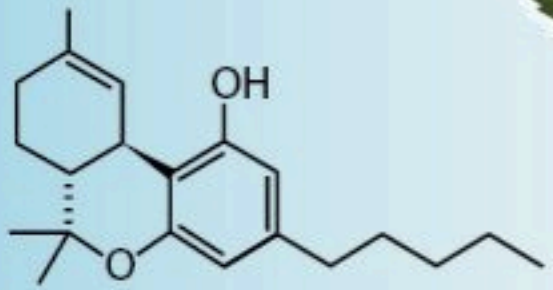
Marijuana use was defined as those responding "yes" to ever using hashish or marijuana. Cardiovascular (CV) disease was defined broadly as those responding "yes" to ever being told by a health care provider they had congestive heart failure, coronary heart disease, or a heart attack. Response rates to both questions ranged from 49.3% to 51.5% throughout the study timeframe. NHANES = National Health and Nutrition Examination Survey.

DeFilippis, E.M. et al. J Am Coll Cardiol. 2020;75(3):320–32.

Psychoactive

Delta 9-
tetrahydrocannabinol

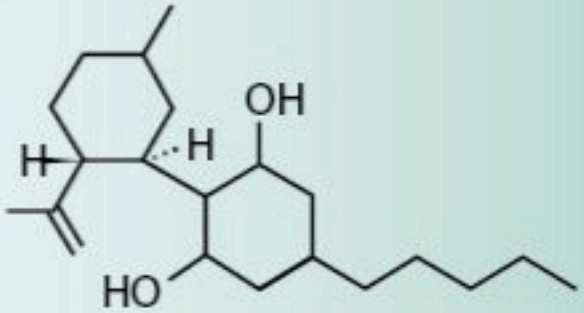
THC



Non-psychoactive

Cannabidiol

CBD



- 400 individual chemicals
- 60 cannabinoids
- Terpenes - chemical compounds found in the fragrant oils of many plants that influence their scents and flavours + other effects

Types of Products and Routes of Use

- Inhalation (smoke or vapor)
  - Onset within minutes
  - Peak conc 30-60 mins
- Oral
  - onset ~1 hour
  - Peak levels 2-3 hrs
  - High first pass; variable response
- Lipid soluble; wide distribution; excretion through feces and urine over $\geq$ 1 week

Many Potential Health Applications

Report

HIGHLIGHTS

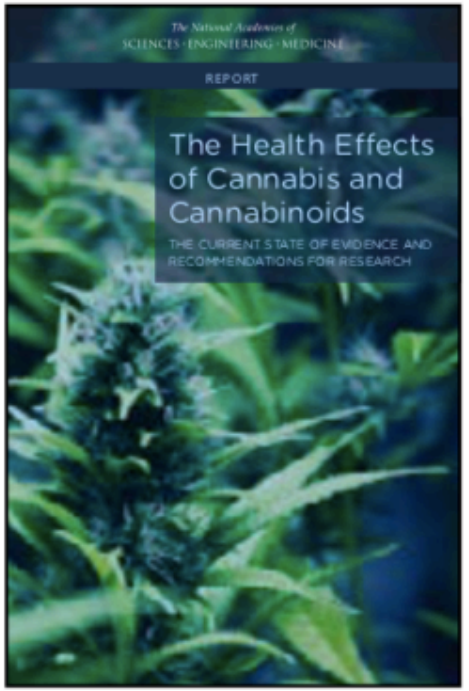
January 2017

National Academies of Sciences, Engineering, and Medicine.

The Health Effects of Cannabis and Cannabinoids

The Current State of Evidence and Recommendations for Research

Recent years have seen a rapid rise in the medical and recreational use of cannabis: a broad term that can be used to describe the various products and chemical compounds (e.g., marijuana, cannabinoids) derived from different species of the cannabis plant. Despite increased cannabis use and a changing state-level policy landscape, conclusive evidence regarding the short- and long-term health effects—both harms and benefits—of cannabis use remains elusive.



Despite increased cannabis use and a changing state-

Is Cannabis Safe for the Heart?

- 65 yo woman with known CAD; occasional cannabis smoker – any CV concerns?

Circulation

AHA SCIENTIFIC STATEMENT

Medical Marijuana, Recreational Cannabis, and Cardiovascular Health

A Scientific Statement From the American Heart Association

ABSTRACT: Cannabis, or marijuana, has potential therapeutic and medicinal properties related to multiple compounds, particularly Δ-9-tetrahydrocannabinol and cannabidiol. Over the past 25 years, attitudes toward cannabis have evolved rapidly, with expanding legalization of medical and recreational use at the state level in the United States and recreational use nationally in Canada and Uruguay. As a result, the consumption of cannabis products is increasing considerably, particularly among youth. Our understanding of the safety and efficacy of cannabis has been limited by decades of worldwide illegality and continues to be limited in the United States by the ongoing classification of cannabis as a Schedule 1 controlled substance. These shifts in cannabis use require clinicians to understand conflicting laws, health implications, and therapeutic possibilities. Cannabis may have therapeutic benefits, but few are cardiovascular in nature. Conversely, many of the concerning health implications of cannabis include cardiovascular diseases, although they may be mediated by mechanisms of delivery. This statement critically reviews the use of medicinal and recreational cannabis from a clinical but also a policy and public health perspective by evaluating its safety and efficacy profile, particularly in relationship to cardiovascular health.

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On behalf of the American Heart Association Clinical Pharmacology Committee and Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Lifestyle and Cardiometabolic Health; and Council on Quality of Care and Outcomes Research

Key Words: AHA Scientific Statements ■ cannabinoids ■ cannabis ■ medical marijuana ■ public health

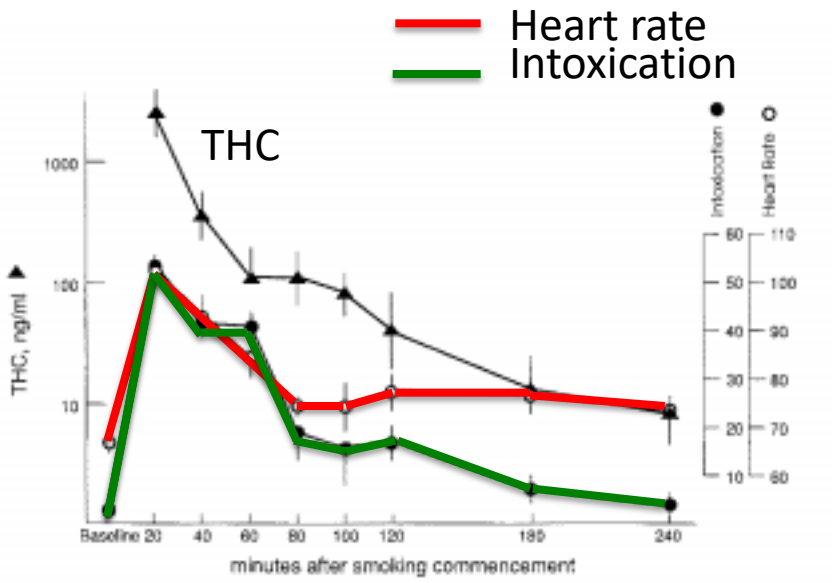
https://www.ahajournals.org/journal/circ

Cannabis has been used since as early as 100 CE for its potential therapeutic and medicinal properties from its multiple compounds, particularly Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Over the past 25 years, attitudes toward the recreational and medicinal use of cannabis have rapidly evolved in the United States from illicit to decriminalized to legalized at the state level (Figure 1A and 1B).[1–4] In addition to national legalization in Uruguay and Canada, other countries have followed suit. In 2019, Thailand became the first nation in Southeast Asia to legalize medical cannabis and removed low-level cannabis and hemp extracts from its list of banned narcotic substances. Mexico has drafted legislation for cannabis legalization currently under review. Other countries that are considering legal changes to cannabis include Colombia, Argentina, Peru, Ecuador, Thailand, the United States, Australia, New Zealand, and Chile (Figure 1A). By 2025, legal cannabis sales are projected to generate $23 billion in the United States. In the United States, cannabis use has risen particularly among those 18 to 25 years of age (Figure 2).[5] This massive shift in policy and use has forced clinicians to critically evaluate the safety and efficacy of cannabis. However, our understanding of the health effects of cannabis has been limited by decades of worldwide illegality and continues to

- Case reports
- Cohorts
- Overviews
- No RCTs

Acute Effects of THC - Physiology

- Increase HR
- Drowsy
- Dry mouth, thirst, nausea
- Hunger or “munchies”
- Headache, dizziness
- Fluctuating temperature
- Euphoria



Menkes et al. Psychopharm 1991;103(2):277–279

- 13 young men paid to smoke a joint!!

The NEW ENGLAND JOURNAL of MEDICINE

EFFECT OF MARIHUANA AND PLACEBO-MARIHUANA SMOKING ON ANGINA PECTORIS

WILBERT S. ARONOW, M.D., AND JOHN CASSIDY, M.D.

Abstract We evaluated the effect of smoking marihuana versus placebo marihuana on cardiovascular function and on exercise-induced angina in 10 patients with angina pectoris. With the subject resting smoking one marihuana cigarette increased the product of systolic blood pressure times heart rate and venous carboxyhemoglobin level and decreased the exercise time until angina 48 per cent. Smoking one placebo marihuana cigarette increased the venous carboxyhemoglobin level, did not affect the product of systolic blood pressure times heart rate of resting subjects, and decreased the exercise time until angina 8.6 per cent. Smoking marihuana significantly decreased the exercise time until angina more than smoking placebo marihuana ($p<0.001$). Smoking marihuana probably increases the myocardial oxygen demand and decreases myocardial oxygen delivery, causing patients with angina to experience agina after exercise sooner, and with less work.
(N Engl J Med 291:65-67, 1974)

Acute Effects - Symptoms

- 10 subjects with angina
- Marijuana vs. “placebo” cigarette
- Increase HR x BP
- Increase carboxyhemoglobin
- Increase myocardial demand; decrease oxygen delivery
- Decrease exercise time to angina by 48%

NEJM 1974

Morbidity and Mortality

- Determinants of Myocardial Infarction Onset Study
  - Acute use – MI relative risk 4.8 [CI 2.4 to 9.5]
  - Chronic - risk of CV mortality over 3.8 years
    - HR 4.2 [CI 1.2 to 14.3] for **≥ 1 / week**
    - HR 2.5 [CI 0.9 to 7.3] for 0 – 1 / week
  - Increased risk for All cause mortality
    - HR 3.0 [CI 1.3 to 7.0] for any use
  - Limitations – ascertainment of exposure; marijuana and tobacco co-use

Mittleman et al. Circulation 2001;103: 2805e2809

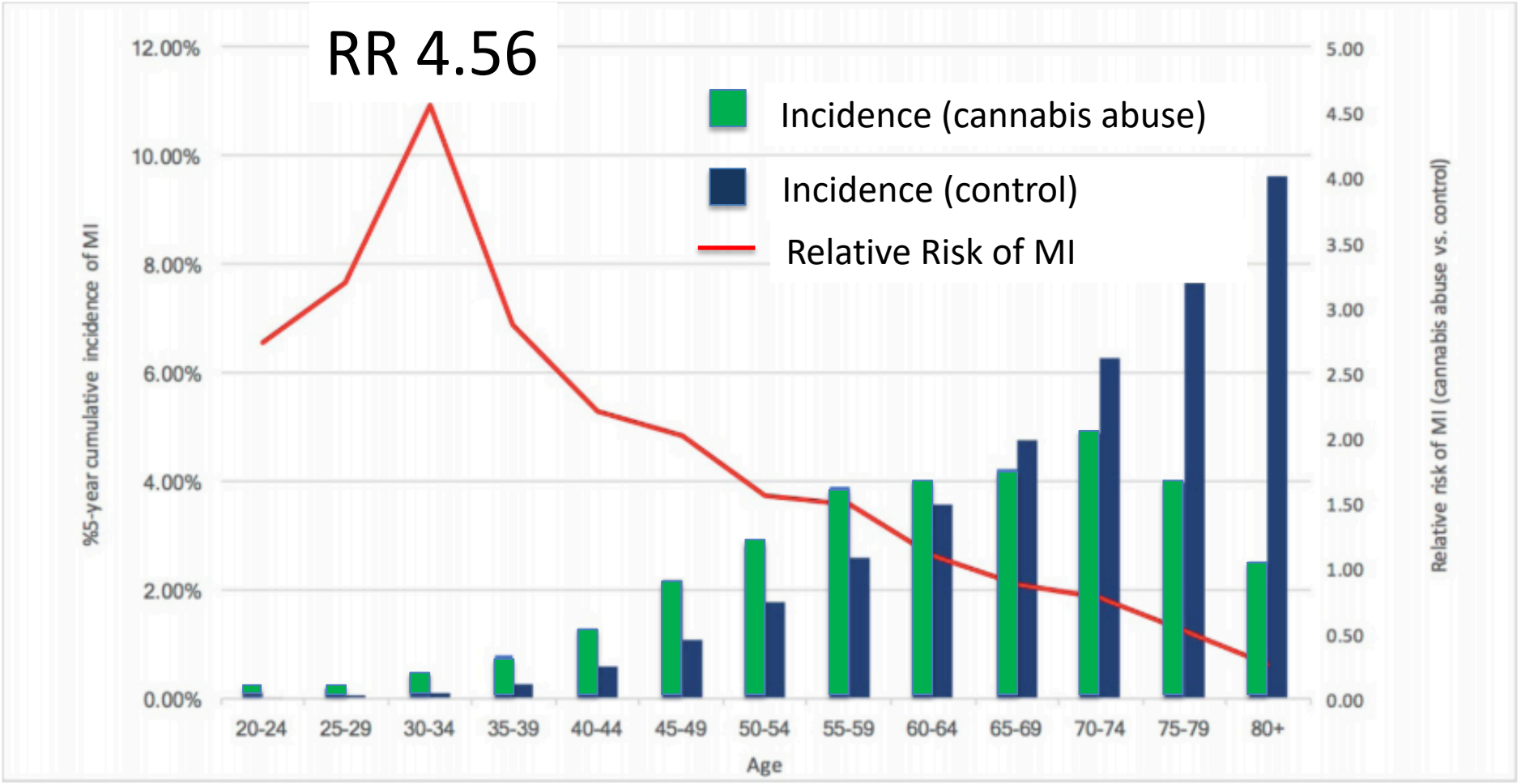
Acute and Stable Ischemic Heart Disease

CANNABIS ABUSE AND RISK FOR MYOCARDIAL INFARCTION: A POPULATION BASED STUDY

Presentation Number: 907-14
Authors: Ahmad Tarek Chami, Chang Kim, Case Western Reserve University, Cleveland, OH, USA

- large, multi-institutional database
- prospective, matched cohorts (2011-2016)
- 210,700 cannabis abusers vs. 10,395,060 age-matched controls
- incidence of MI was significantly higher in the cannabis group: odds ratio **1.72** [1.67-1.77]

CANNABIS ABUSE AND RISK FOR MYOCARDIAL INFARCTION: A POPULATION BASED STUDY



Unusual Cardiac Risk in Young

- 35 yo man
- Chest pain after smoking joint
- ECG shows widespread **ischemia**
- Echo shows odd features of **“heart ballooning”**

Unusual Cardiac Risk in Young - Marijuana and Stress Cardiomyopathy

- National Inpatient Sample, 33,343 patients admitted for **Takotsubo** syndrome from 2003 to 2011; of these, 210 patients were active marijuana users
- marijuana use was an independent predictor of Takotsubo (**odds ratio 1.99**, 95% CI 1.72–2.32; P<0.0001).
- more often **younger men and fewer CV risk factors** vs. non marijuana users

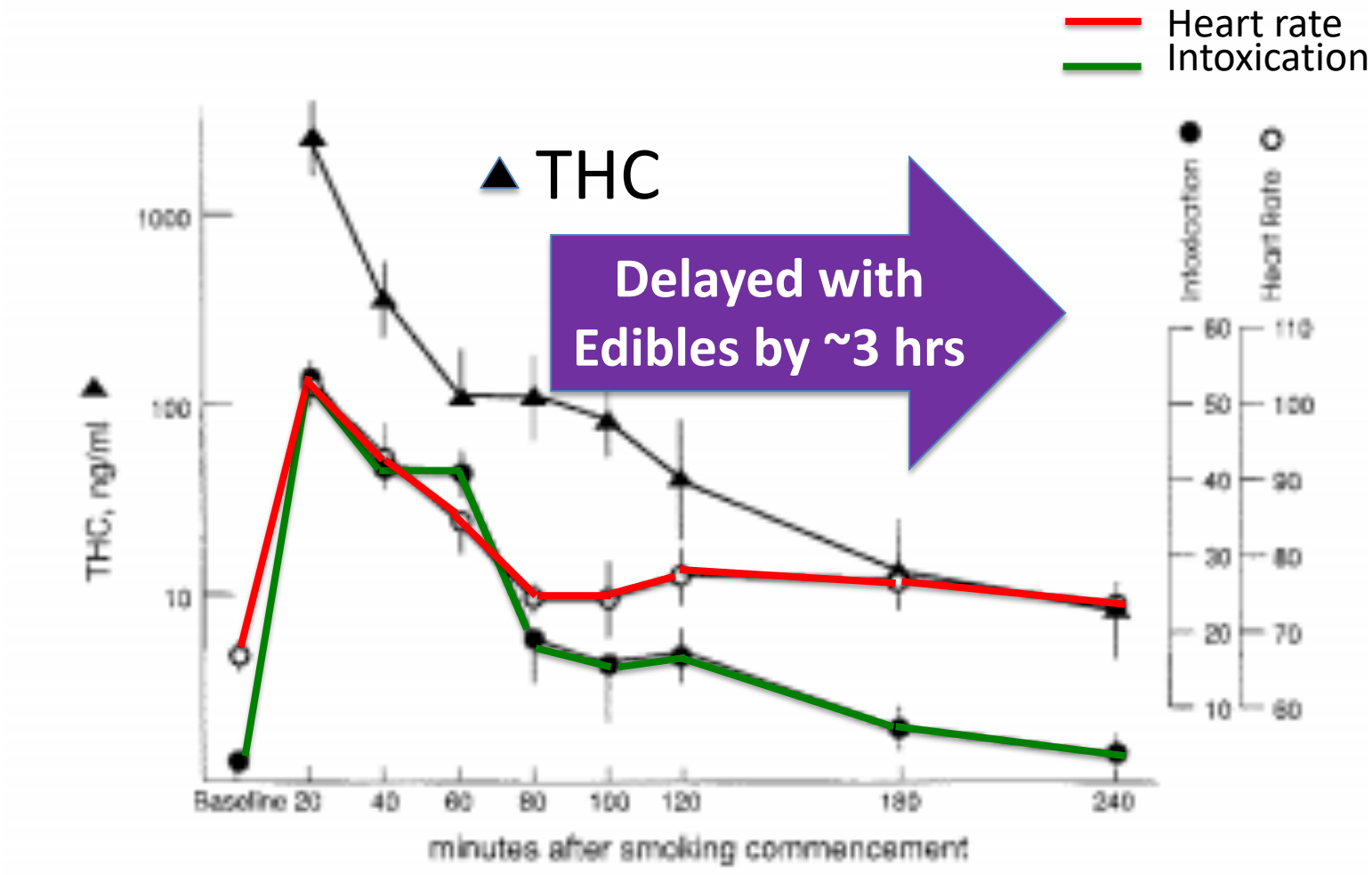
Singh A, et al. AHA 2016 Scientific Sessions; Nov 2016; New Orleans, LA. Abstract S4054

Insidious Cannabis Story

- 75 yo man 6 mos post MI – admitted to hosp with delirium and tachycardia – is this cannabis related??

Concern re: cannabis edibles

Acute Effects of Smoked THC



Menkes et al. Psychopharm 1991;103(2):277–279

Annals of Internal Medicine ORIGINAL RESEARCH

Acute Illness Associated With Cannabis Use, by Route of Exposure

Table 2. Most Common Clinical Conditions Associated With Cannabis-Attributable Visits, Stratified by Route of Exposure

Condition	Edible Exposure (n = 238), n (%)	Inhalable Exposure (n = 2329), n (%)	Absolute Difference (Edible − Inhalable) (95% CI), *percentage points*	Total Visits, n (%)
Gastrointestinal symptoms	36 (15.1)	752 (32.3)	−17.2 (−12.2 to −22.1)	788 (30.7)
[illegible]	[illegible]	[illegible]	[illegible]	440 (17.1)
Intoxication	115 (48.3)	647 (27.8)	20.5 (13.9 to 27.1)	762 (29.7)
[illegible]	[illegible]	[illegible]	[illegible]	633 (24.7)
Acute psychiatric symptoms	43 (18.0)	254 (10.9)	7.1 (2.1 to 12.1)	297 (46.9)
Acute exacerbation of underlying chronic disease	1 (0.4)	93 (4.0)	−3.6 (−2.5 to −4.7)	94 (14.1)
[illegible]	[illegible]	[illegible]	[illegible]	100 (15.8)
Cardiovascular symptoms	19 (8.0)	73 (3.1)	4.9 (1.4 to 8.4)	92 (3.6)

- Intoxication
- Acute psychiatric
- CV symptoms

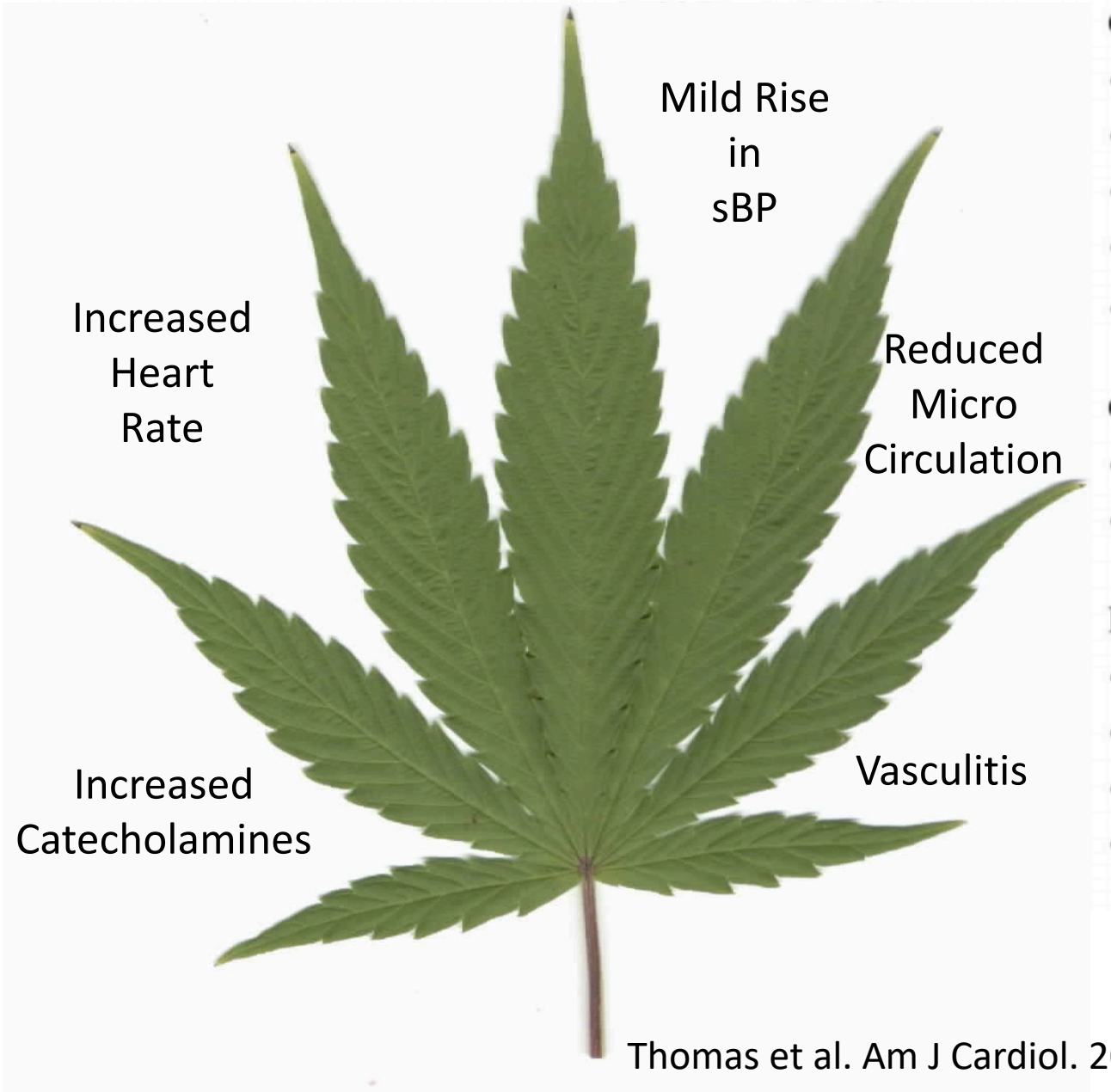
Monte et al. Ann Intern Med March 26,2019
University of Colorado Emerg Dept

Arrhythmia Story

- 34- year-old man developed syncope and ventricular tachycardia after marijuana use.
- In the EP lab, VT was inducible.
- Coronary angiography showed normal coronary arteries with a significant reduction in coronary flow.
- Reversible after cessation of marijuana

Rezkalla et al. Ann Emerg Med 2003;42:365e369

Summary of Adverse CV Effects



CARDIOVASCULAR

- increased angina frequency
- myocardial infarction
- cardiac death
- cardiomyapathy
- arrhythmia

CEREBROVASCULAR

- fransient ischemic attack
- strokes

PERIPHERAL

- thromboangitis obliterans
- Raynaud's Phenomenon
- ischemic ulcer
- digital necrosis

Thomas et al. Am J Cardiol. 2014 Jan 1;113(1):187-90

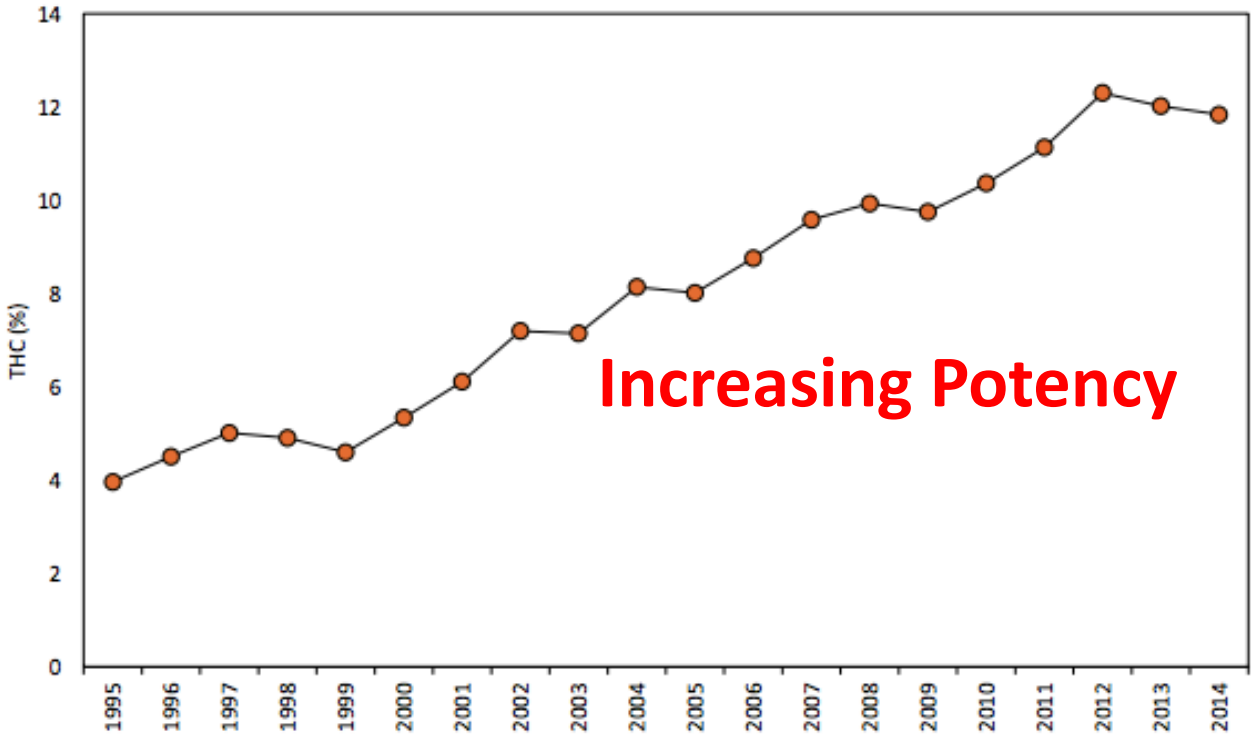
Are there other concerns?

Changes in Cannabis Potency Over the Last 2 Decades (1995–2014): Analysis of Current Data in the United States

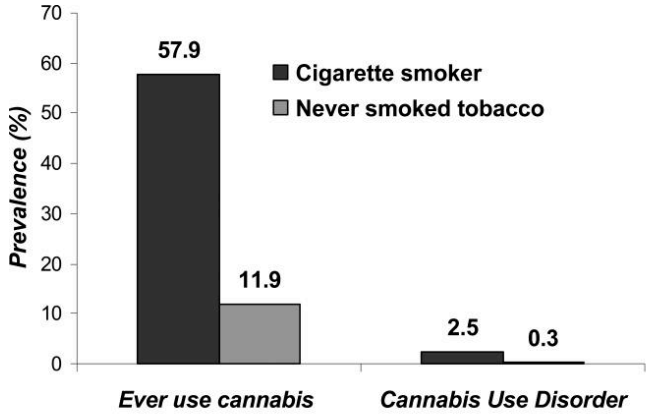
Mahmoud A. ElSohly, Zlatko Mehmedic, Susan Foster, Chandrani Gon, Suman Chandra, and James C. Church

Biological Psychiatry 2016;79:613-619

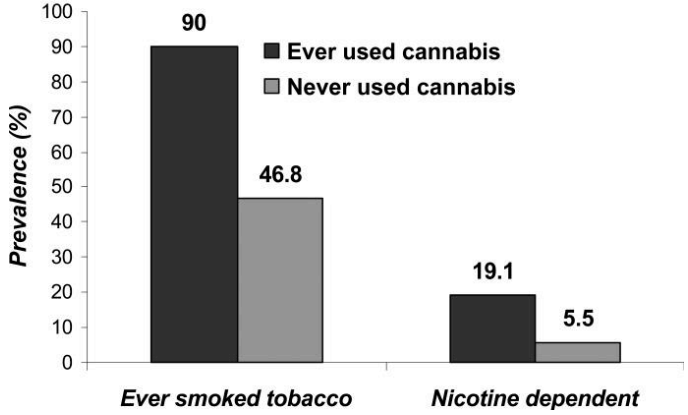
- **THC** conc. in DEA specimens
- n= 38,861



Strong Co-Relationship – Cannabis and Tobacco



Many Smokers are tokers



Most Tokers are smokers

Agrawal et al. Addiction. Jul 2012; 107(7): 1221–1233.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

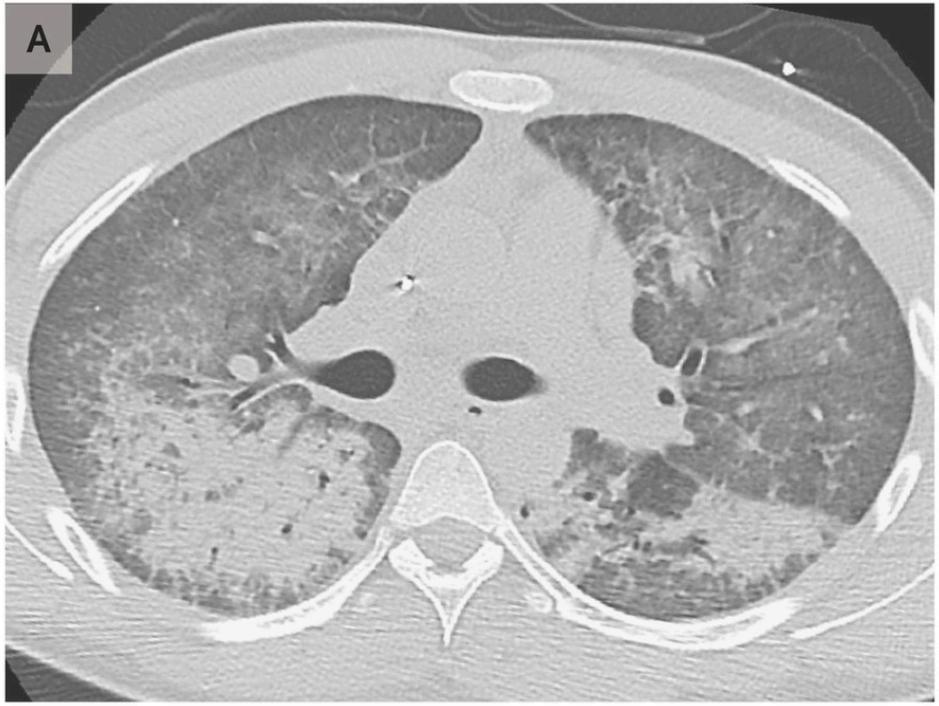
Adverse Health Effects of Marijuana Use

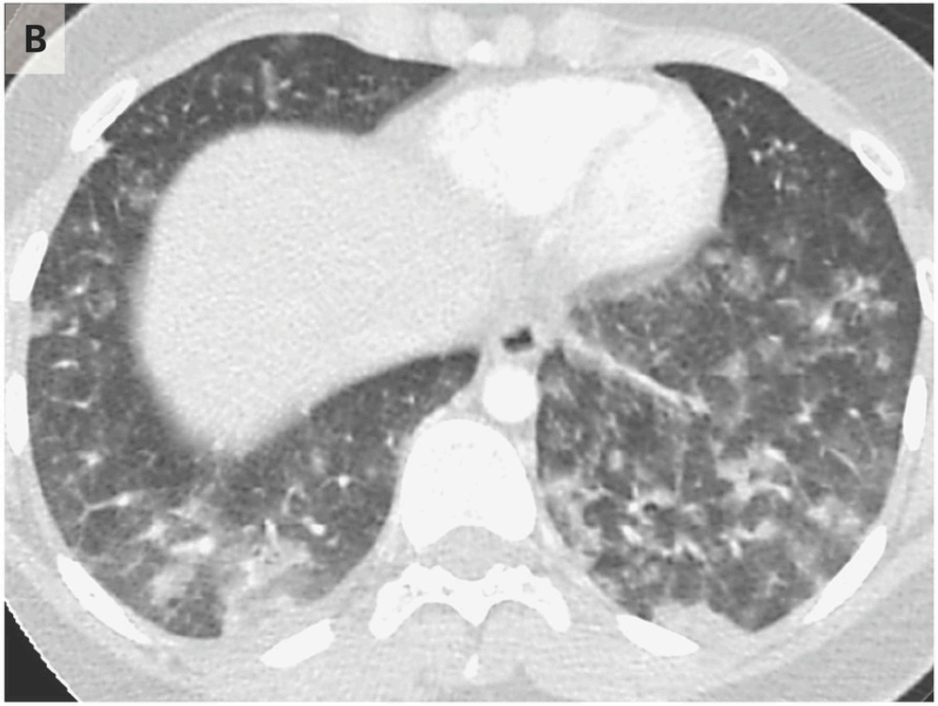
Nora D. Volkow, M.D., Ruben D. Baler, Ph.D., Wilson M. Compton, M.D., and Susan R.B. Weiss, Ph.D.

- Increased Airway Resistance
- Hyperinflation of Lungs
- Chronic Bronchitis
- Increased Rates of Infection
- Cancer? (Studies are equivocal)

Volkow et al. N Engl J Med 2014;370:2219-27

E-cigarette and Vaping associated Acute Lung Injury (EVALI)

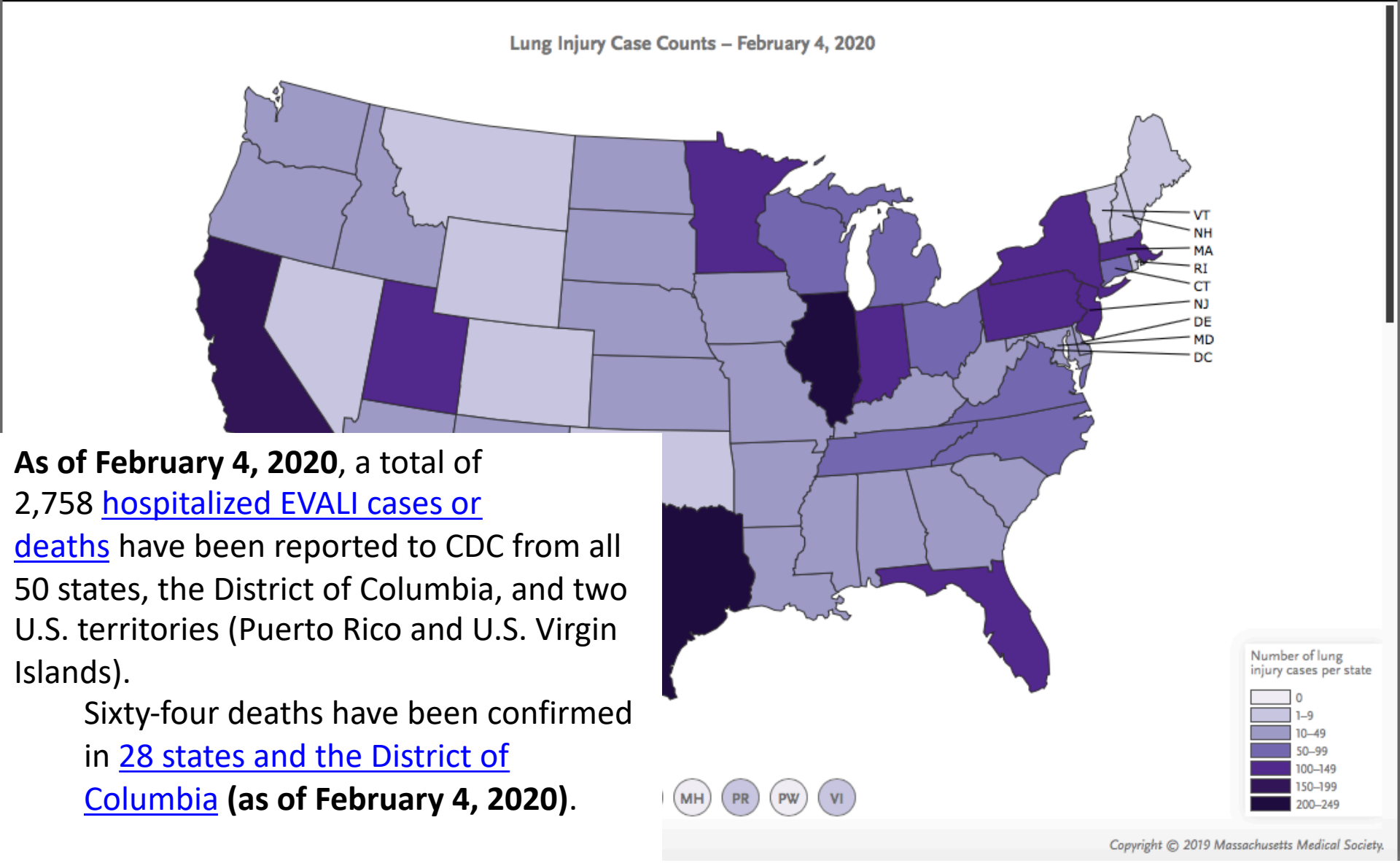




- 20-year-old man with diffuse alveolar damage (Panel A)
- 19-year-old woman with acute eosinophilic pneumonia (Panel B)
- Consolidation, ground-glass opacity, bronchial dilatation and alveolar damage.
- Some respond to steroids

N Engl J Med 2019; 381:1486-1487

Lung Injury Associated with Electronic Cigarettes, or Vaping



As of February 4, 2020, a total of 2,758 hospitalized EVALI cases or deaths have been reported to CDC from all 50 states, the District of Columbia, and two U.S. territories (Puerto Rico and U.S. Virgin Islands).

Sixty-four deaths have been confirmed in 28 states and the District of Columbia **(as of February 4, 2020)**.

https://interactives.nejm.org/ile/cdc_vaping/index.html

Smoking & Tobacco Use

Home > Basic Information > Electronic Cigarettes

Home

Office on Smoking and Health (OSH)

Quit Smoking

Basic Information

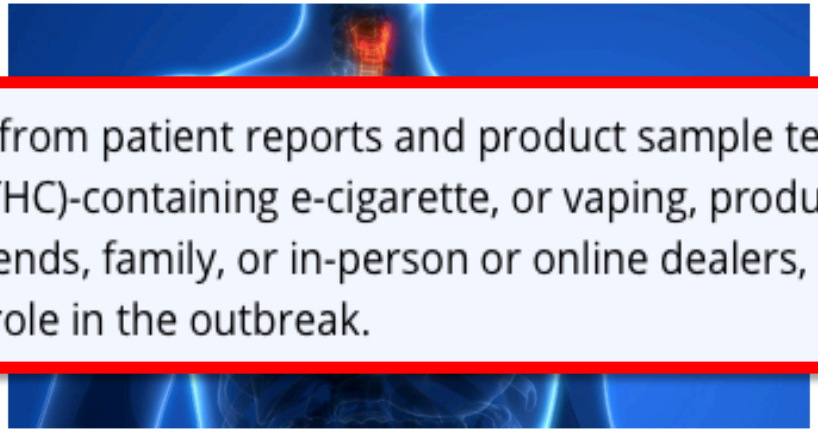
About Electronic Cigarettes (E-Cigarettes)

Quick Facts on the Risks of E-cigarettes for Kids, Teens, and Young Adults

Outbreak of Lung Injury Associated with

Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products

Español (Spanish)



- National and state data from patient reports and product sample testing show tetrahydrocannabinol (THC)-containing e-cigarette, or vaping, products, particularly from informal sources like friends, family, or in-person or online dealers, are linked to most EVALI cases and play a major role in the outbreak.

CDC, the U.S. Food and Drug Administration (FDA), state and local health departments, and other clinical and public health partners are investigating a national outbreak of e-cigarette, or vaping, product use-associated lung injury (EVALI).

For Healthcare

Resources

Digital Press Kit

https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html

Cannabis – Complex Pharmacology

- 70 yo woman
- Post CABG and mechanical AVR
- Migraine headaches; painful neuropathy; hypertension; poor sleep; “stress”
- What is the best “pot” for me?

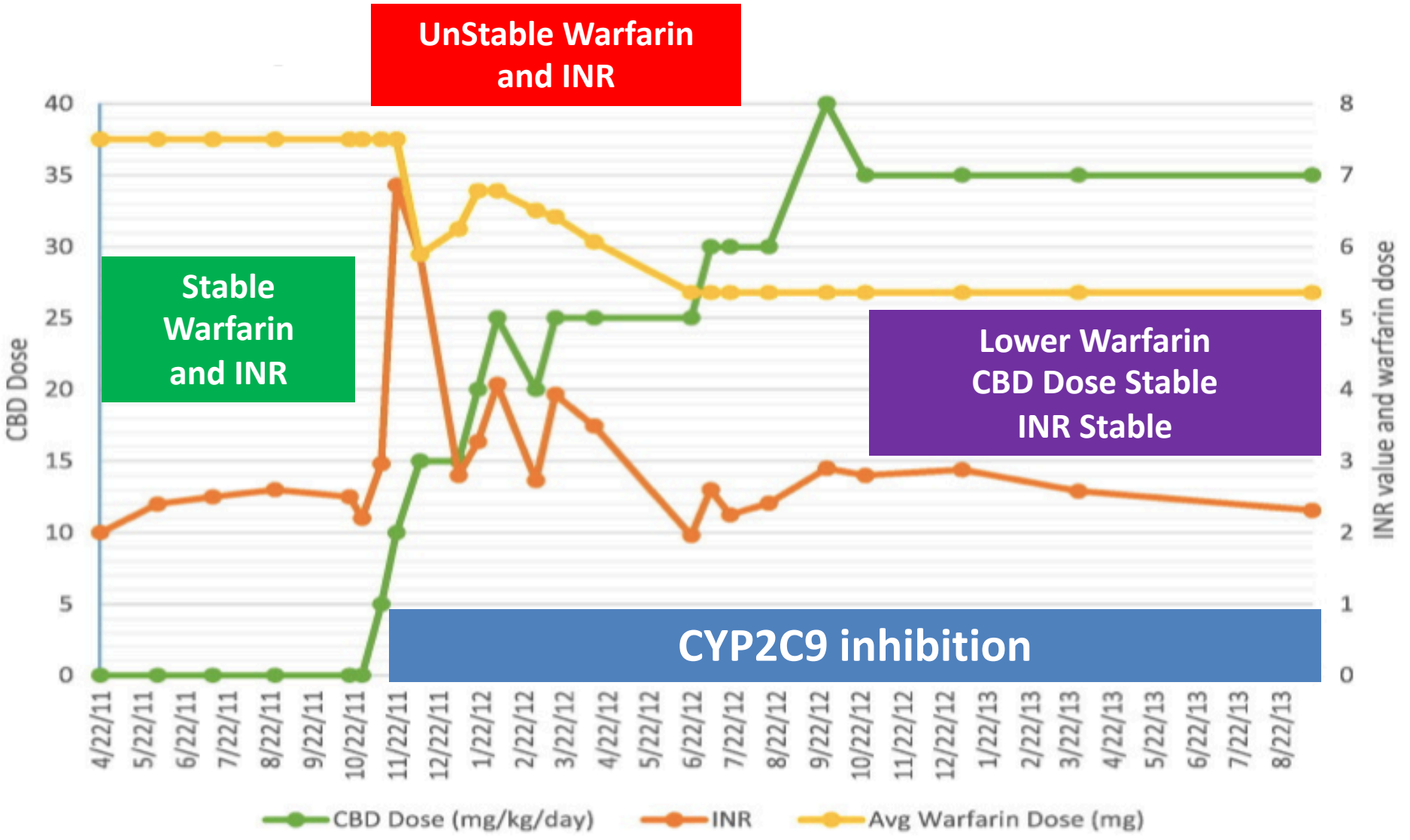
ASA 81 mg OD
Metoprolol 25 mg BID
Amlodipine 5 mg OD
Simvastatin 40 mg OD
Amitriptyline 50 mg qhs
Acetaminophen + codeine
Warfarin ~5 mg OD

Cannabis and drug interactions

- **THC and CBD are metabolized by CYP3A4**
- **CBD is a potent inhibitor of:**
  - **CYP3A4** calcium channel blockers, benzodiazepines, cyclosporine, some statins
  - **CYP2D6** SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids

Flockhart 2007, Watanabe et al 2007, Yamaori et al 2012

Case: Warfarin – CBD Interaction



Grayson et al. Epilepsy Behav Case Rep. 2018; 9: 10–11.

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TABLE 4 Medications Affected by Cannabinoids (10,14,63,77)

Mechanism	Cannabinoid Involved	Key Therapy Affected	Anticipated Change in Drug Level
CYP3A4 inhibition	CBD, THC, CBN, SCB	Antiarrhythmic (amiodarone, quinidine, lidocaine)	↑
		Calcium-channel blockers (dihydropyridine + nondihydropyridine)	↑
		Isosorbide dinitrate/mononitrate	↑
		Statins (atorvastatin, lovastatin, simvastatin)	↑
CYP2C9 inhibition	CBD, THC, CBN, SCB	Warfarin	↑
		Statins (rosuvastatin, fluvastatin)	↑
		Nonsteroidal anti-inflammatory drugs (celecoxib, ibuprofen, naproxen)	↑
CYP2D6 inhibition	CBD, THC, CBN	Beta-blockers (carvedilol, metoprolol)	↑
		Antiarrhythmic (flecainide, mexiletine, propafenone)	↑
CYP1A inhibition/induction	CBD, CBN, SCB	Theophylline, caffeine	Inhibition: ↑ Induction: ↓

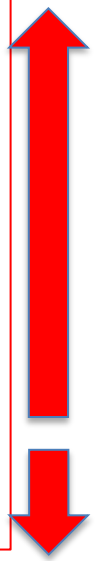
↑ = increase; ↓ = decrease; CBD = cannabidiol; CBN = cannabinol; SCB = synthetic cannabinoids; THC = delta-9-tetrahydrocannabinol.

DeFilippis, E.M. et al. J Am Coll Cardiol. 2020;75(3):320–32.

Complex Pharmacotherapy

- *What is the best "pot" for me*??

ASA 81 mg OD
Metoprolol 25 mg BID
Amlodipine 5 mg OD
Simvastatin 40 mg OD
Amitriptyline 50 mg qhs
Warfarin 5 mg OD
Acetaminophen + codeine

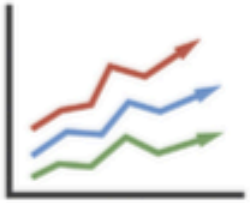


Potential Interactions with CBD:

- Slow pulse
- Low blood pressure
- Muscle aches
- Abnormal rhythm
- Increased INR
- More pain

Summary

Awareness



- >2 million Americans with CV disease are estimated to have used marijuana
- Marijuana use has been associated with a broad range of adverse CV risks
- Potency of marijuana has been ↑ over time, linked with ↑ in vaping and synthetic cannabinoids

Screening

- Screen especially in enriched populations (states with prevalent use, young patients)
- Inquire about concurrent drugs of abuse
- Ask about frequency, quantity, and methods of administration

Patient Discussion

- Review CV therapies with pharmacist to clarify pharmacological interactions
- Acknowledge limited scope of science and potential CV risks

Scientific Research

- Broad commitment of the scientific community to pursue marijuana-related research to clarify CV safety profile

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