



## *Implications of Marijuana Decriminalization on Respiratory, Critical Care and Sleep*

National Association for Medical Direction of  
Respiratory Care (NAMDRC): 2017 Conference  
The Meritage Resort, Napa CA  
24<sup>th</sup> March, 2017  
9.30am-10.15am

Ivor S. Douglas, MD  
Denver Health Medical Center &  
U Colorado, Denver  
idouglas@dhha.org




## **American Thoracic Society Marijuana Workgroup**

- Ivor S. Douglas (Co-chair)
- Timothy E. Albertson
- Patricia Folan
- Nicola A. Hanania
- Donald P. Tashkin
- Dona J. Upson
- Frank T. Leone (Co-chair)



*We help the world breathe*  
PULMONARY • CRITICAL CARE • SLEEP



## ISD Disclosures

Grant support to Denver Health Medical Center

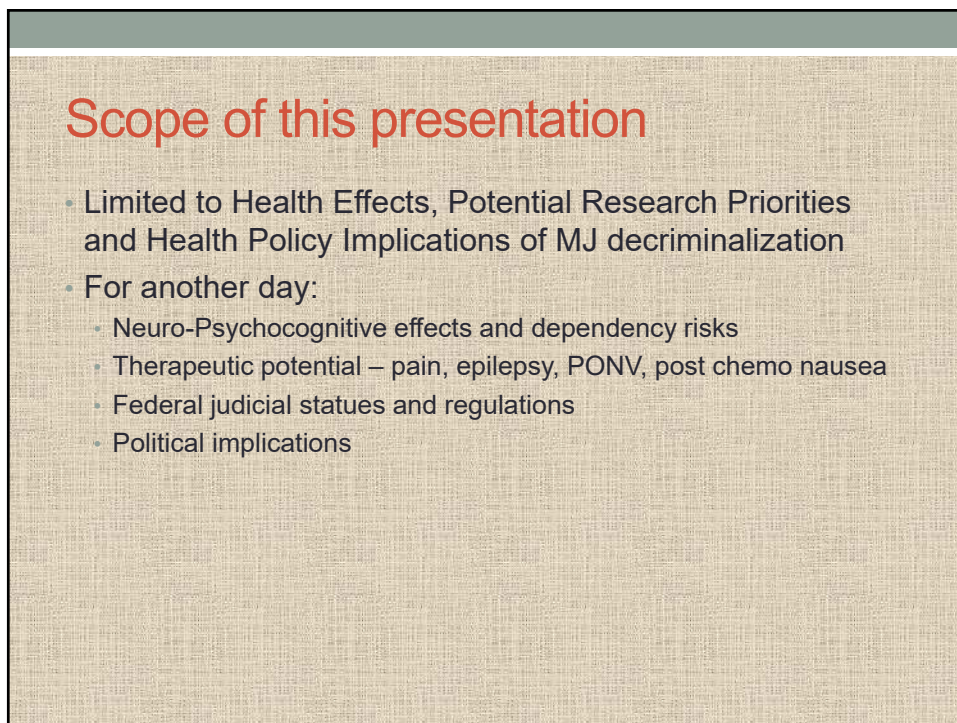
- NIH-NIAID R01 2015-2020
- No Tobacco industry funding

## ISD Disclaimers

- Non user; Non ideological
- Concern regarding continued politicization (and near-complete limitation) of Federal **research funding** regarding human health implications
- Concern for **social consequences** and impact of increased and ready availability of high THC concentration MJ to teens and children with developing brains
- Concern that decriminalization is leading to widespread **social normalization** without adequate quantification of potential human health impact (risks and potential benefits)
- Interest in potential impact on **concomitant or future opiate, alcohol and other substance use or dependence**



- **Respiratory Impacts of MJ Use/Misuse**
- Limited impact on respiratory function with occasional use
- Significant and frequent use associated with chronic bronchitis symptoms independent of concomitant tobacco smoking
- Low probability of carcinogenicity independent of concomitant tobacco smoking
- Substantial and immediate need for Federal and local funding of high quality mechanistic, clinical and epidemiological research to characterize impact on human health.



## Scope of this presentation

- Limited to Health Effects, Potential Research Priorities and Health Policy Implications of MJ decriminalization
- For another day:
  - Neuro-Psychocognitive effects and dependency risks
  - Therapeutic potential – pain, epilepsy, PONV, post chemo nausea
  - Federal judicial statues and regulations
  - Political implications

## A “Legitimate” Medical Compound

- Listed in U.S Pharmacopeia 1850-1941
  - marijuana & hashish extracts were the 1st, 2nd, or 3rd most prescribed meds in the US from 1842-1890s



## MJ in the US: Advancing to Decriminalization

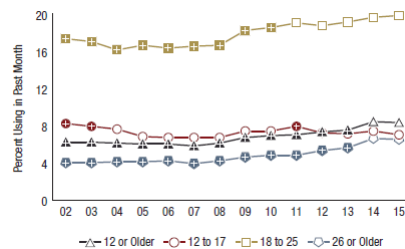
- 1971 Post Vietnam “War on drugs”
  - President Richard M. Nixon announced the appointment of Dr. Jerome H. Jaffe as Special Consultant to the President for Narcotics and Dangerous Drugs.
- “America’s public enemy number one in the United States...” pledging to “fight and defeat this enemy... [by] wag[ing] a new, all-out offensive.”
- Congress provided legislative authority and funds for a “worldwide offensive dealing with the problems of sources of supply” as well as rehabilitation, research, and education.
- A major focus of this war was directed at marijuana cultivation, distribution, and use.

## Winning the Battles, Losing the War?

- Policy positions late '80s
  - Testimony (without high quality science) from doctors and seriously ill patients that MJ eased pain, reduced nausea of chemotherapy, reversed anorexia of AIDS, preserved vision of glaucoma victims.
- 1996 California first state to legalize medical marijuana
- 2009 U.S. Justice Department announced that federal prosecutors would not pursue medical marijuana users and distributors,
- 2012: Colorado and Washington legalized recreational marijuana use for adults (regulated retail sales 2014).
  - 2015 Alaska, Oregon, and Washington, D.C.
- 2013: Uruguay first country to legalize marijuana

## Widespread MJ Usage

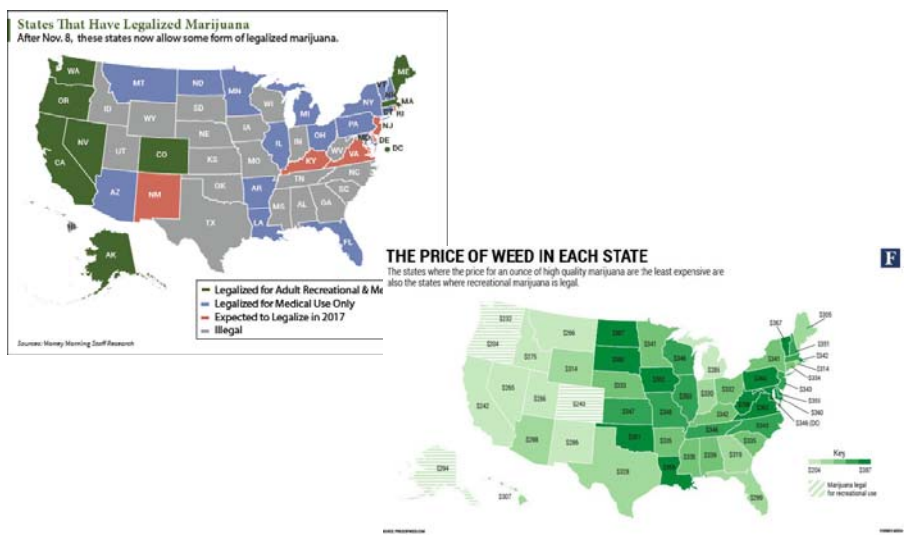
- 2015 National Survey on Drug Use and Health from the Substance Abuse and Mental Health Services Admin.
  - 22.2 million Americans, current users
    - 7.0% of children 12 to 17
    - 19.8% 18 to 25
    - 6.5% adults > 26 years
  - 40.3% of current users (5.4 million) daily or near daily.



## U.S. Justice Department: Office of National Drug Control Policy

- “Marijuana is a topic of significant public discourse in the United States, and while many are familiar with the discussion, it is not always easy to find the latest, research-based information on marijuana to answer the common questions about its health effects, or the **differences between Federal and state laws** concerning the drug.
- “**Confusing messages** being presented by popular culture, media, proponents of “medical” marijuana, and political campaigns to legalize all marijuana use perpetuate the false notion that marijuana is harmless.
- “This significantly **diminishes efforts to keep our young people drug free** and hampers the struggle of those recovering from addiction.”

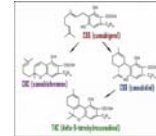
## US States Legalizing MJ for “Medicinal” and Recreational Use.





## Cannabis ~ MJ ~ THC

- Marijuana: dried leaves and flowering tops of hemp plant
  - *Cannabis sativa*
  - *Cannabis indica* and *Cannabis ruderalis*
- Smoked in non-filtered “joint” hand-rolled cigar
  - 250 to 1,000 mg.
  - Vs. regular cigarette : larger puff & inhaled volumes  
5x longer breath-holding times
  - 4x greater tar deposition
- Major psychoactive: delta-9-tetrahydrocannabinol (THC)
  - varies widely between plants
  - increased substantially  
3.4% (1993) → 8.8% (2008) → 10%?



## Alternative Combustible MJ, Delivery Devices

- “Spliff” or a “kiff”: Marijuana + tobacco
- Hashish: waxy resin contained within the glandular hairs (trichomes) of the marijuana plant
  - high THC concentration. Smoked using a pipe or hookah
  - marijuana vaporizers,
  - vape pens.
- Blunts: hollowed-out cigars, or leaf tobacco, filled with MJ
- “Bong” smaller and portable
- Water pipe: hookah with a bowl, stem, and water container.
  - Particulate ingredients not removed by the water.
- Tabletop vaporizers → pyrolysis (<~230°C).
  - Vapor containing active cannabinoids devoid of particulates

## Components of MJ Smoke and Acute Effects on Airway Dynamics

- Volatile and particulate phase components similar – MJ and tobacco
  - MJ >60 cannabinoid compounds
  - **Gas phase:** carbon monoxide, ammonia, hydrocyanic acid, isoprene, acetaldehyde, formaldehyde, acrolein, dimethylnitrosamine, and methylethyl nitrosamine,
  - **Particulate phase:** phenols, polycyclic aromatic hydrocarbons (PAHs), including benzo[a]pyrene, benz[a]anthracene, phenol, and naphthalene.
- MJ smoke - perceived benefit recommended for asthma, 19C.



## Components of MJ Smoke and Acute Effects on Airway Dynamics

- Dose-dependent bronchodilation: volunteers and asthma patients
  - Superior to nebulized isoproterenol, persisted > 1 hour.
  - Acute exposure to MJ protects against acute bronchospasm
  - Reverses chemically induced and exercise-induced bronchospasm
- Bronchodilatation: stimulation of prejunctional cannabinoid-type 1 (CB1) receptors on efferent vagal nerves in the airway
  - Blocks acetylcholine release
  - Irritant effects of cigarette smoke induces acute bronchospasm by stimulating airway cholinergic reflex mechanisms.



## Effects of inhaled marijuana on lung function and disease

Lung Disorder or Disease	Association and Confounders
Airway disease, chronic bronchitis symptoms	Increased chronic bronchitis symptoms and airway inflammation; likely nonadditive with concomitant tobacco smoking

- Bronchoscopy: Bronchitis (erythema, edema, increased secretions) common in MJ, MJ + tobacco smokers vs. nonsmokers.
- Endobronchial biopsies: pathology mainly confined to the larger central airways - ↑ number and size of submucosal blood vessels, submucosal edema, inflammatory cell infiltrates, hyperplasia of mucus-secreting surface epithelial (goblet) cells.
- Additive abnormalities in MJ + tobacco smokers

*Taylor DR, Addiction 2000;95:1669–1677.*  
*Tashkin DP, Am Rev Respir Dis 1987;135:209–216.*  
*Tan WC, CMAJ 2009;180:814–820.*  
*Bloom JW, Br Med J (Clin Res Ed) 1987;295:1516–1518.*  
*Aldington S, Thorax 2007;62:1058–1063.*  
*Roth MD, AJRCCM 1998;157:928–937*

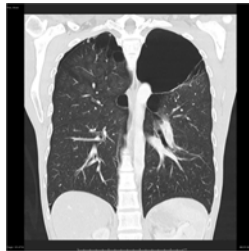
## Effects of inhaled marijuana on lung function and disease

Lung Disorder or Disease	Association and Confounders
COPD and impaired lung function	Minimal impairment in light and occasional moderate users when controlled for tobacco use. Effects in heavier, regular users incompletely quantified

- Slight ↓ in FEV1/FVC (Taylor, '00; Bloom, '87)
- No ↓ in FEV1/FVC, after adjusting for tobacco smoke exposure (Tashkin, '80 & '87; Tan, '09; Aldington, '07; Hancox, '10)
- A significant ↑ FVC may cause spurious reduction in ratio. (Hancox, '10)
- Non significant ↓ FEV1 in heaviest users over 20y.

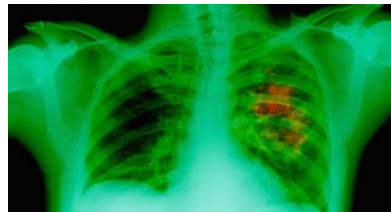
## Association between marijuana smoke exposure and decrease in FEV1/FVC

- HRCT scans in 75 MJ alone, 91 MJ and tobacco, 92 tobacco alone, 81 nonsmoking subjects (Aldington, '07)
  - Small significant  $\uparrow$  in low lung apical attenuation in MJ alone and MJ+ tobacco users, suggesting enlarged air spaces.
  - ? bullous changes
- Long-term effects in moderate, persistent MJ smokers of different ages and sexes remains to be definitively determined.



## Effects of inhaled marijuana on lung function and disease

Lung Disorder or Disease	Association and Confounders
Lung and aerodigestive cancers	Significantly increased premalignant histopathological and molecular changes in airway epithelia. However, only minimal to slightly increased risk for lung and aerodigestive malignancies in light and moderate users when controlled for tobacco smoking. Effects in heavier, regular users incompletely quantified



## Procarcinogenic Chemicals and Dysplasia

- PAHs, benzo[a]pyrene, and benz[a]anthracene,
  - Similar to those found in tobacco smoke
  - MJ smoked in lower amounts than tobacco
    - prolonged breath-holding time & reduced filtration → fourfold increase in the respiratory deposition of PAH-containing tar.
- Premalignant dysplasias increased
- Bronchial biopsies significantly increased expression of molecular markers of pretumor progression,
  - epidermal growth factor receptor mutations
  - Ki-67 (nuclear proliferation protein),
- Young persons (<40–45y) with lung and upper airway cancer - high proportion of regular MJ smokers.

## No Epidemiological Linkage with Cancer

- 5 year case-control study Los Angeles county 18 to 59y
  - Risk of aerodigestive malignancies, including lung cancer
  - 611 lung cancer cases
    - 311 (51%) were MJ ever-smokers,
    - 183 had a cumulative lifetime history of > 10 joint-years.
  - 1,040 control subjects
    - 561 (54%) were MJ ever-smokers
    - 115 had a cumulative lifetime history of > 10 joint-years.
- No association in adjusted analysis for any level of MJ exposure
  - Age and sex as covariates
  - adjustments for race, educational level, tobacco, and alcohol
  - 0-1 joint yr: Adjusted OR 0.63 (95% CI, 0.46–0.87)
  - >60 joint yr: Adjusted OR 0.62 (95% CI, **0.32–1.2**)
- Strong association between tobacco and aerodigestive cancers

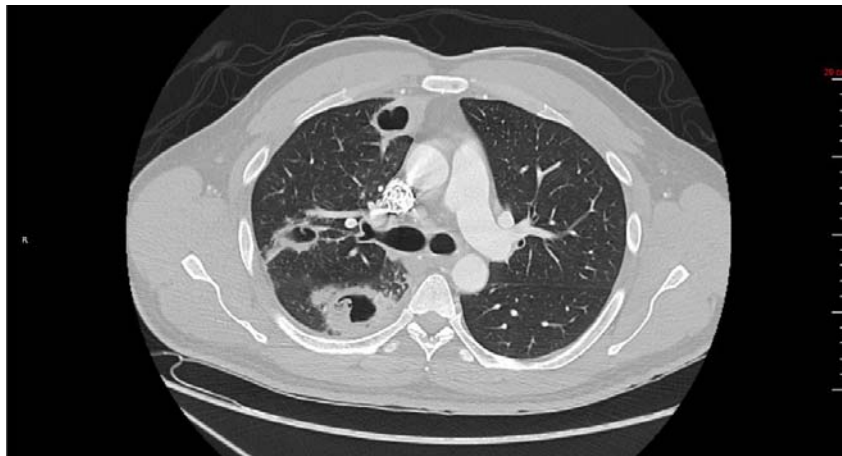
*Hashibe M, Cancer Epidemiol Biomarkers Prev 2006; 15:1829–1834.*

## Effects of inhaled marijuana on lung function and disease

Lung Disorder or Disease	Association and Confounders
Lower respiratory tract infections	THC impairs airway mucociliary function and macrophage host-innate immune responses. Possible increased risk of <i>Aspergillus fumigatus</i> and MTB infections in immunocompromised patients, including HIV/AIDS

- Impairs fungicidal and bactericidal activity of alveolar macrophages
- Impairs lung's defense against microbial infection
- Impairs mucociliary clearance → excess airway accumulation of mucus → substrate for colonizing microbes.
- MJ frequently contaminated with *A. fumigatus* & potentially pathogenic gram-negative bacteria → may increase PNA risk.

## Cavitating Fungal Pneumonia - Young DM Male



## Effects of inhaled marijuana on lung function and disease

Lung Disorder or Disease	Association and Confounders
Lung barotrauma	Associated with deep or forcible inhalation but association potentially confounded by concomitant tobacco smoking

- Pneumothorax or pneumomediastinum
  - Deep inhalation technique + long breath-holding time with Valsalva
  - “Shotgunning”: inhaling smoke (frequently, crack cocaine or marijuana) and then forcibly exhaling into another individual’s mouth
    - participants with differing lung vital capacity esp women recipients of a larger man’s exhaled breath
- Large lung bullae (may be more common in MJ + tobacco smokers)

## Respiratory Consequences of MJ

**Substantial statistical evidence:**

- Worse respiratory symptoms and more frequent chronic bronchitis episodes

**Moderate statistical evidence:**

- Improved airway dynamics with acute use, but not with chronic use
- Higher forced vital capacity (FVC)

**Moderate statistical evidence** between the cessation of cannabis smoking and:

- Improvements in respiratory symptoms

**Limited statistical evidence:**

- An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking)

**No or insufficient evidence** to support or refute an association:

- Hospital admissions for COPD
- Asthma development or asthma exacerbation

## Ingested Cannabinoids (Edibles)

- Edibles/Medibles: Cannabinoids, marijuana extracts and cannabis hash oil,
  - baked cookies and brownies, chewing gums, tinctures (alcohol-glycerin-based extractions), drinks, candy delicacies, chocolates
  - Ingested doses vary significantly - standardized unit dosing (10 mg/unit in Colorado). Single brownie ~ 6 to 10 unit doses.
  - Variable absorption: intoxicating effects delayed 40 - 60 min after ingestion. Repeated ingestion (“stacking”)
- Cyclic vomiting syndrome: Naïve users, Cannabis tourists
- Synthetic cannabinoids, cannabicyclohexanol: spice, K2, or black mamba,
  - Local epidemics of severe potentially fatal systemic illness; hypermania, seizures, autonomic instability, and renal failure

## Cannabinoids and Sleep

- Common reason legally and illicitly. (1/4 High school users)
  - Inconsistent and confusing findings.
  - sleep onset latency increased, no change
  - Deep (slow-wave) sleep increased, decreased or no change
  - REM sleep increased, decreased or no change
- THC 15 mg ± CBD 15 mg, or THC 5 mg ± CBD 5 mg
  - no significant effects of THC alone on any measure of sleep.
  - “Morning after” sleepiness increased.
  - Higher-dose THC plus CBD increased morning-after sleepiness, reduced deep sleep, and increased the duration of wakefulness
    - THC may be sedative and hypnotic
    - CBD is alerting.
  - Inhaled or ingested cannabis - variable quantities expected to produce variable effects on sleep and wakefulness.



## Cannabis withdrawal

- Significant effects on sleep process. 1 to 3 days after discontinuation, may persist for weeks.
  - Difficulty sleeping
  - PSG of withdrawal increased sleep latency, reduced deep sleep, and increased dreaming sleep.

## Injury and Death

Substantial statistical evidence:

- Increased risk of motor vehicle crashes

Moderate statistical evidence:

- Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal

No or insufficient evidence to support or refute association:

- All-cause mortality (self-reported cannabis use)
- Occupational accidents or injuries (general, non-medical cannabis use)
- Death due to cannabis overdose



## Basic mechanism gaps

### Preclinical gaps

- Effects of THC and other cannabinoids on aerodigestive and respiratory **epithelial homeostasis** and cellular biology
- Cellular, molecular (including epigenetic), and organ level **effects of marijuana inhalation and ingestion**,
  - Potential synergistic pro- and anticarcinogenic effects with tobacco smoke and nicotine
- Cellular and molecular effects of marijuana **mainstream and sidestream smoke** in preclinical models of lung development, lung cancer, COPD, and chronic bronchitis

## Basic mechanism gaps

- **Additive or potentially synergistic effects** of co-inhalation of ammonia, hydrogen cyanide, NO, and NO<sub>x</sub> than comparable cigarette smoke
- Evaluation of effects of inhaled MJ smoke, ingested marijuana and extracts, and other endocannabinoid receptor agonists on **host and adaptive immune responses** to infection and injury.
  - Specifically alteration in immune responses to mycobacterial, fungal, and viral pathogens

## Basic mechanism gaps

Pathophysiology and clinical gaps

- **Clinical toxicology** studies with commercially available high THC concentration marijuana strains
- Neuropsychiatric and cardiovascular pathophysiological effects of **synthetic cannabinoids**

## Basic mechanism gaps

- Controlled evaluations of **potential clinical therapeutic** effects of cannabinoids, including THC and cannabidiol (CBD), for neuropsychogenic, epileptic, and pain syndromes
- Clinical, pathological, and neuropsychiatric effects of **prolonged and high-frequency usage** on adult lung function and chronic lung disease initiation and development, sleep architecture and disorders, and acute and critical illnesses
- Controlled clinical studies of **clinical effects of inhaled (smoked and vaporized), ingested, and topical** ingestion of marijuana including standardized laboratory and commercial strains
- Controlled study of the potential additive and synergistic effects of marijuana inhalation or ingestion with tobacco smoke or **vaporized nicotine (e-cigarettes)**

## MJ-tobacco COPD link:

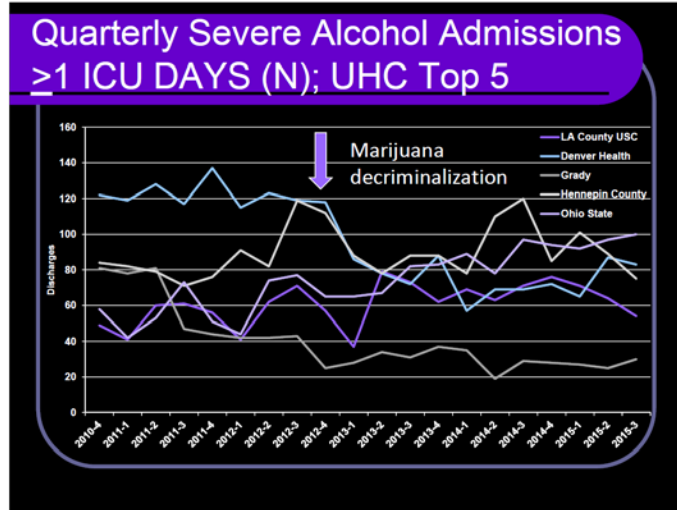
- Studies to definitively evaluate causal associations between marijuana smoking and the onset or progression of COPD are urgently needed to inform public health and policy positions.

Absent evidence of illness is NOT equivalent to evidence of absent illness,

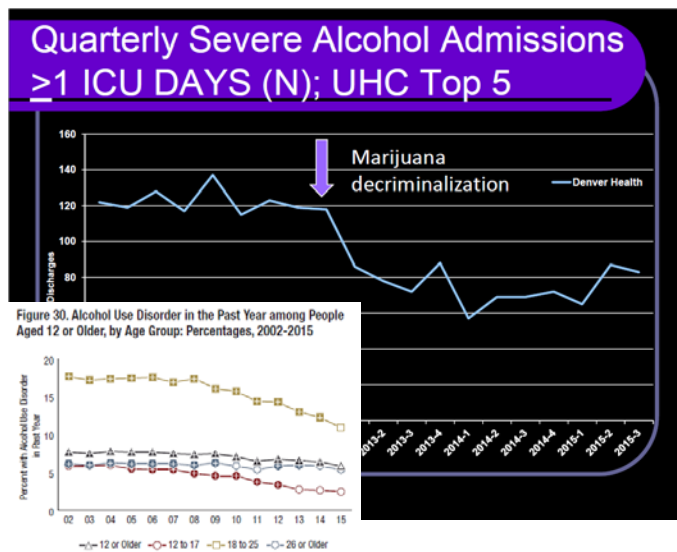
## MJ Carcinogenesis

- Unlike the robust evidence for tobacco, the nature of the relationship between marijuana smoke exposure and the change in carcinoma risk over time, as well as the specific mutations and histopathology to expect, remain unknown.

## ICU Discharges – Alcohol Admission



## ICU Discharges – Alcohol Admission



## Public Health and Policy Recommendations

1. Evaluate the effects of **decriminalization on youth consumption**.
2. Determine the public health impact and consequences of **unit dose standardization** for edible and inhaled forms of marijuana.
3. Assess the effects of decriminalization on **concomitant tobacco, e-cigarette, and other substance use** and dependence.

## Public Health and Policy Recommendations

4. Evaluate the impact of decriminalization on **public health measures**, including public consumption of tobacco, e-cigarettes, alcohol across age groups, sexes, geographic areas, and ethnic/racial groups.
5. Ascertain the impact of decriminalization on **health care costs, accidental trauma** (including motor vehicle and firearm associated injuries), and acute care use and costs.
6. Monitor and advocate for **regulation of commercial and marketing efforts**, particularly by multinational tobacco, food, and beverage companies.
7. Advocate for and monitor the **efficacy of accidental exposure harm-reduction strategies**, including child-resistant packaging, clear and truthful constituent labeling, prominently displayed guidance on how to respond to potential emergencies.





## What Can (and Should) NAMDRRC and Professional Respiratory Societies Do?

5. Advocate on behalf of preserved indoor air quality. In the absence of data on the risks of environmental marijuana smoke, organizations should consider advocating for indoor smoking restrictions for marijuana that are at least as restrictive as those commonly in place for tobacco.
6. Professional medical societies are obligated to avoid the many missed opportunities learned through confronting tobacco corporations' decades-long campaign to delegitimize scientific evidence of harm while challenging regulation and aggressively marketing dangerous tobacco products to vulnerable and youthful consumers.

## Now I Know Why.....



QUESTIONS?

?

[idouglas@dhha.org](mailto:idouglas@dhha.org)  
for lecture hand-  
outs