

somewhat  
different

# Underwriting between Hay and Grass

How to stratify Marijuana Use risk

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*hannover* **re**<sup>®</sup>

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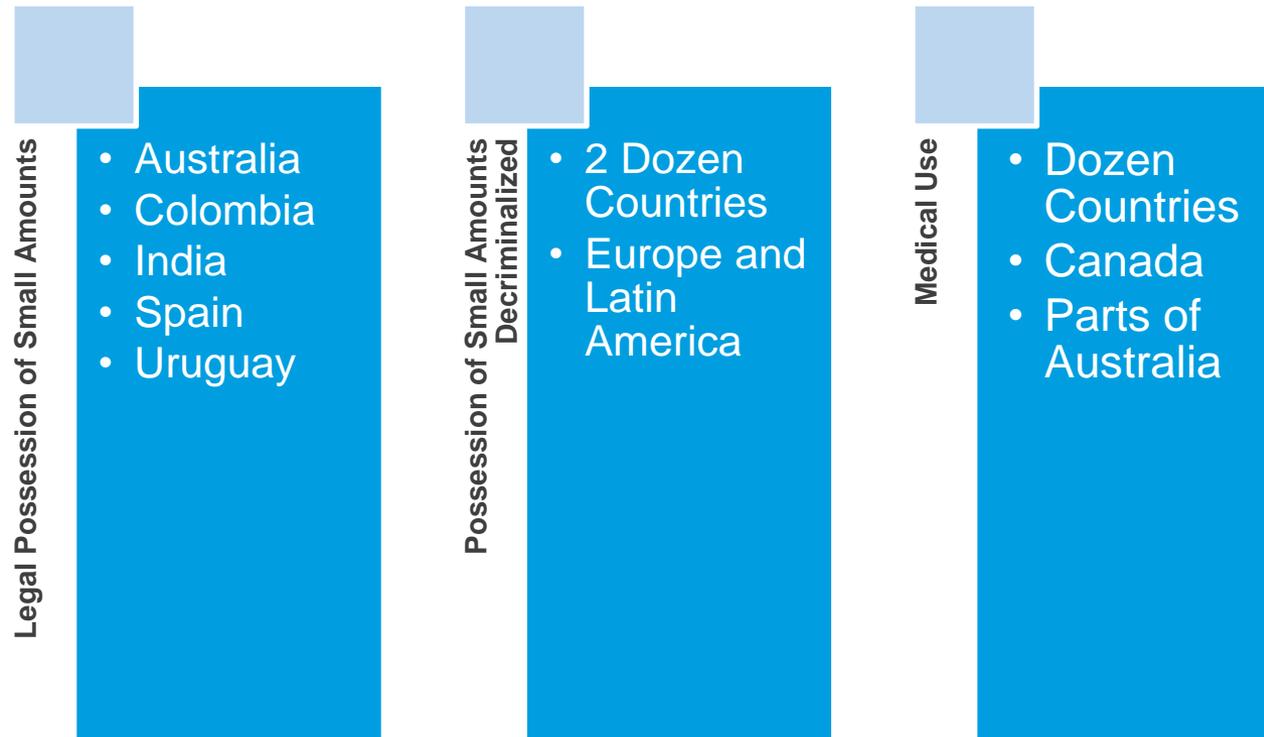
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# Background

- ▶ Marijuana is most commonly used “illicit” drug in USA
  - ~ 12 Million admitted users in 2014
  - 182 Million users worldwide (2016)
- ▶ 4.1 million people (aged 12 years or older) met DSM IV criteria for Marijuana Use Disorder (MUD) in 2014
  - Doubling from 2001/2002 to 2012/2013
- ▶ Marijuana use in adolescence predicts ↑ risk of MUD and other drug use in adulthood

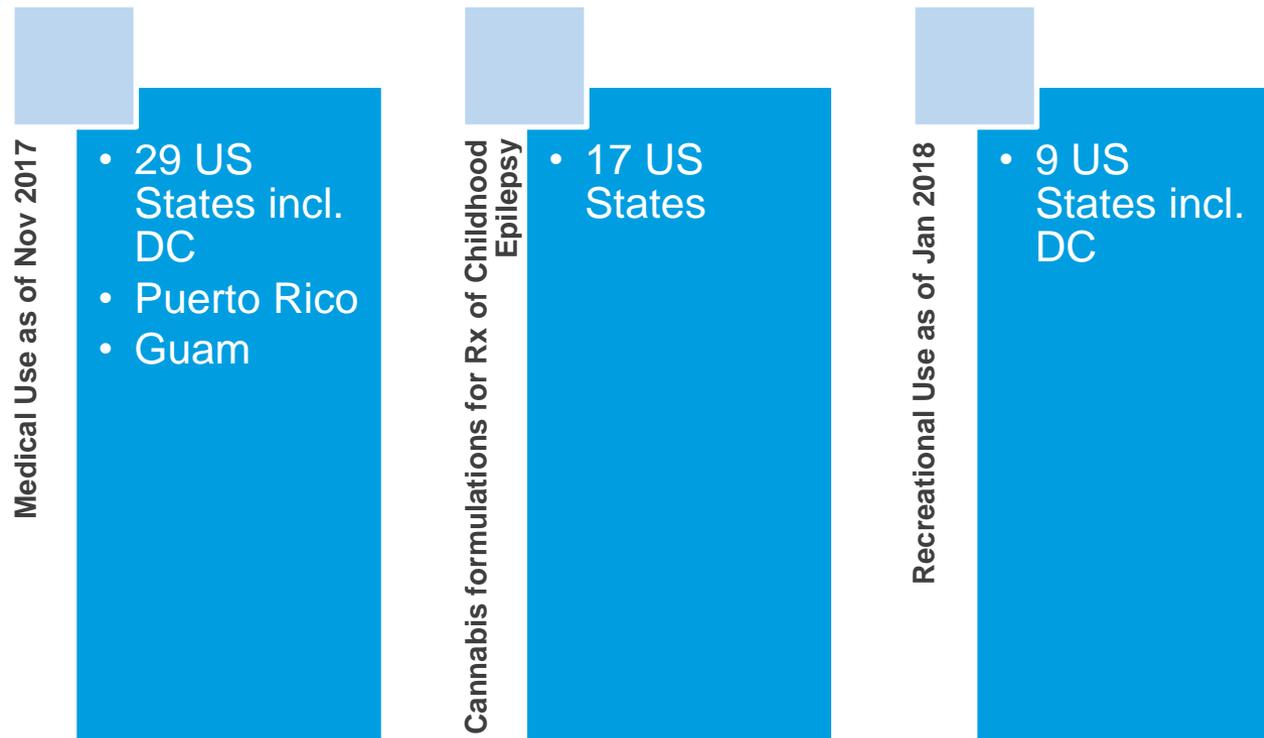
# Varied International Medico-Legal Landscape

- ▶ Legal status of Marijuana varies widely internationally



# Blurred US Medico-Legal Landscape

- ▶ Medico-legal status in the USA is complex



# Changing Medico-Legal Landscape

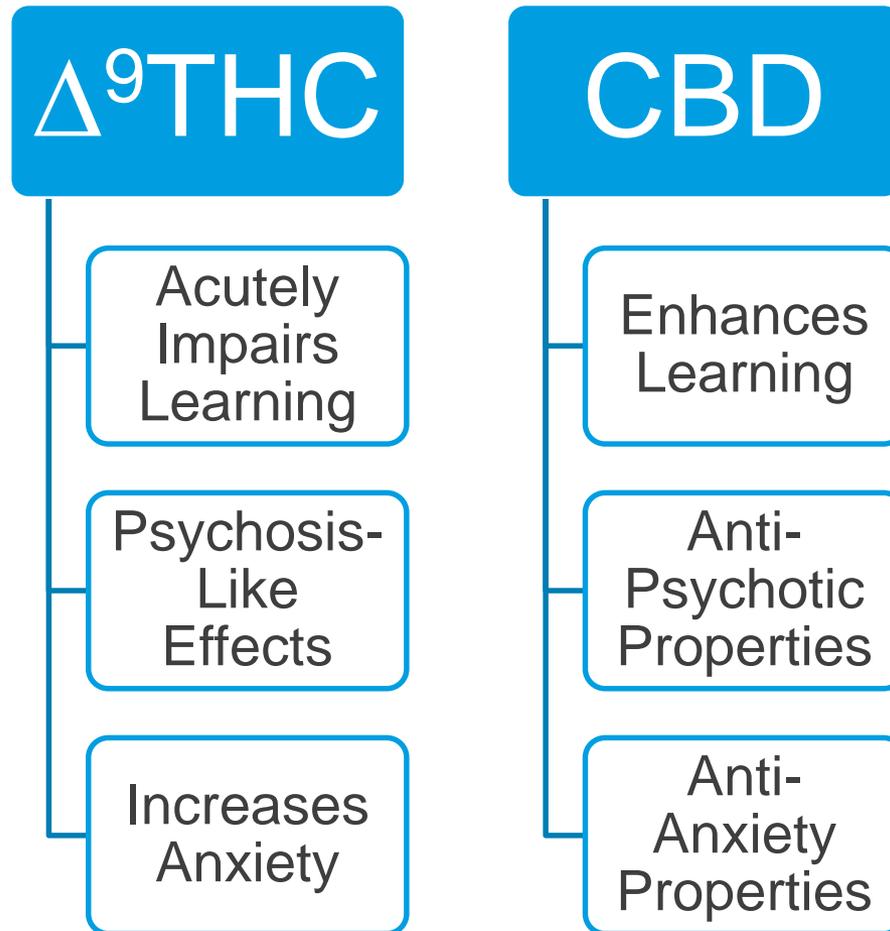
## What does it mean?

- ▶ How patterns of use will change as the legalization of Marijuana proliferates is not known
- ▶ Are we now able to use existing evidence about the less desirable effects of Marijuana use to help us to look forward to the future?

# Marijuana Metabolites

- ▶ ~ 100 unique Cannabinoids in Marijuana
- ▶ Most research focused on 2 Cannabinoids in particular
  - $\Delta$ 9-tetrahydrocannabinol ( $\Delta$ 9-THC)
  - Cannabidiol (CBD)
- ▶ These two compounds seem to have a range of opposing effects on the human brain and behavior

# Marijuana Metabolites

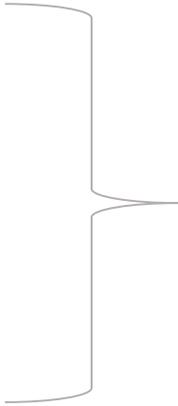


# Marijuana Metabolites

- ▶ Over the past two decades:
  - $\Delta$ 9-THC content of street cannabis has risen dramatically
  - CBD content has decreased to negligible levels
- ▶ In the United States  $\Delta$ 9-THC content of street cannabis rose from 4% in 1995 to 12% in 2014
- ▶ In Europe and Australia high-potency cannabis containing ~15%  $\Delta$ 9-THC and less than 0.1% CBD now dominates the market
- ▶ Type of cannabis available years ago differs considerably from that sold today, limiting the relevance of older longitudinal cohort studies

# Marijuana and the Human Body

- ▶ Study of the Cannabis Sativa plant → Discovery of a remarkable endogenous cannabinoid control center of neurobiological function within humans
- ▶ The human endocannabinoid system extends far and wide within the body as a physiologic modulator including:
  - Central and autonomic nervous system
  - Immune system
  - GIT
  - Reproductive system
  - Cardiovascular system
  - Endocrine network



**“Ubiquitous Network”**

# Marijuana and the Human Body

- ▶ Two CB receptors in the human body
  - CB1 – binds THC. First cloned in 1990
  - CB2 discovered thereafter
  - Disparate distributions and functions
- ▶ Endogenous ligand corresponding to THC
  - Anandamide (discovered in 1992)
  - Binds to CB1
  - Compared to Anandamide that acts like a delicate chisel ingested THC acts like a sledgehammer
- ▶ The near absence of CB1 receptors in the brainstem which is why lethal overdose does not appear to be a concern in humans

# Marijuana and the Human Body

## ▶ CB1

- Found in CNS – psychoactive effects
- Wide distribution in the GIT – regulation of food intake,

## ▶ CB2

- Only in the periphery – intrinsic to cellular and humoral responses related to neuro-inflammation and pain
- Also involved in GIT functions digestion and host defense

# Marijuana Testing

- ▶ Urine testing → Tests for metabolites
  - Duration when test can be positive varies depending on cutoff level used, amount of drug absorbed and frequency of use
    - Usually 1-3 days for acute use
    - Up to a month or more for chronic users → due to fat solubility of the drug
- ▶ Blood testing and oral fluid → tests for both parent drug and metabolites (blood) or metabolites (oral fluid)
  - Up to 1-2 days for heavy users
- ▶ Hair → Tests for metabolites
  - Can be positive up to 90 days

# Does Marijuana Use Increase the Risk Of Death?

- ▶ Systematic Literature Review: 19 papers
- ▶ Published in 2010
- ▶ Studies from 1990 to 2008

# Does Marijuana Use Increase the Risk Of Death?

2 Studies on All-Cause Mortality

9 Studies on Cancer

4 Studies on MVA

4 Studies on Suicidal Behaviors

# Does Marijuana Use Increase the Risk Of Death?

## Marijuana and All-Cause Mortality

- ▶ Kaiser Permanente Medical Program 10 year study of mortality and cannabis users aged 15-49 years
  - Small association with premature mortality **RR of 1.3**
  - Limitations duration of follow up and average age of follow up only 43
- ▶ Swedish study of cannabis use and mortality over 15 years in male military conscripts.
  - Increased risk of premature death in men who had smoked cannabis > 50 times before age 18 but
    - this association disappeared after multivariate adjustment for alcohol and other drug use

# Does Marijuana Use Increase the Risk Of Death?

## Marijuana and All-Cause Mortality

- ▶ The limited available evidence does not indicate an increased risk of mortality for cannabis users in the general population.
- ▶ Relationship between cannabis and all-cause mortality remains unclear

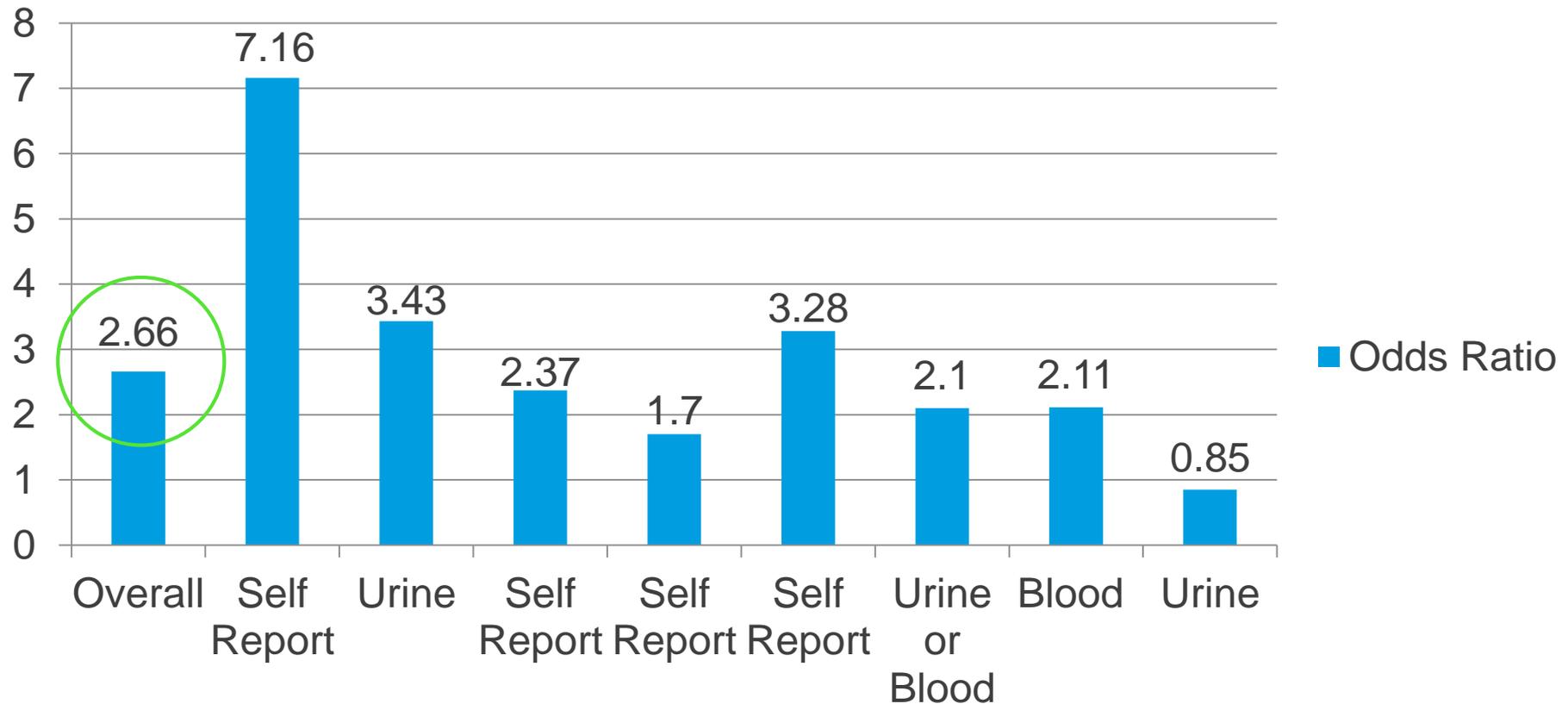
# Does Marijuana Use Increase the Risk Of Death?

## Marijuana and Motor Vehicle Accidents

- ▶ The effect of recreational doses of cannabis on driving shown to be similar to that of blood alcohol content between 0.07% to 0.10%
- ▶ Modest associations found by 3 case control studies comparing detection of THC with drug- and alcohol-free drivers
- ▶ Drivers who had higher levels of THC detected (5 ng/mL) had an increased risk of culpable driving
- ▶ Heavy cannabis use is associated with greater risk of culpable driving than light cannabis use

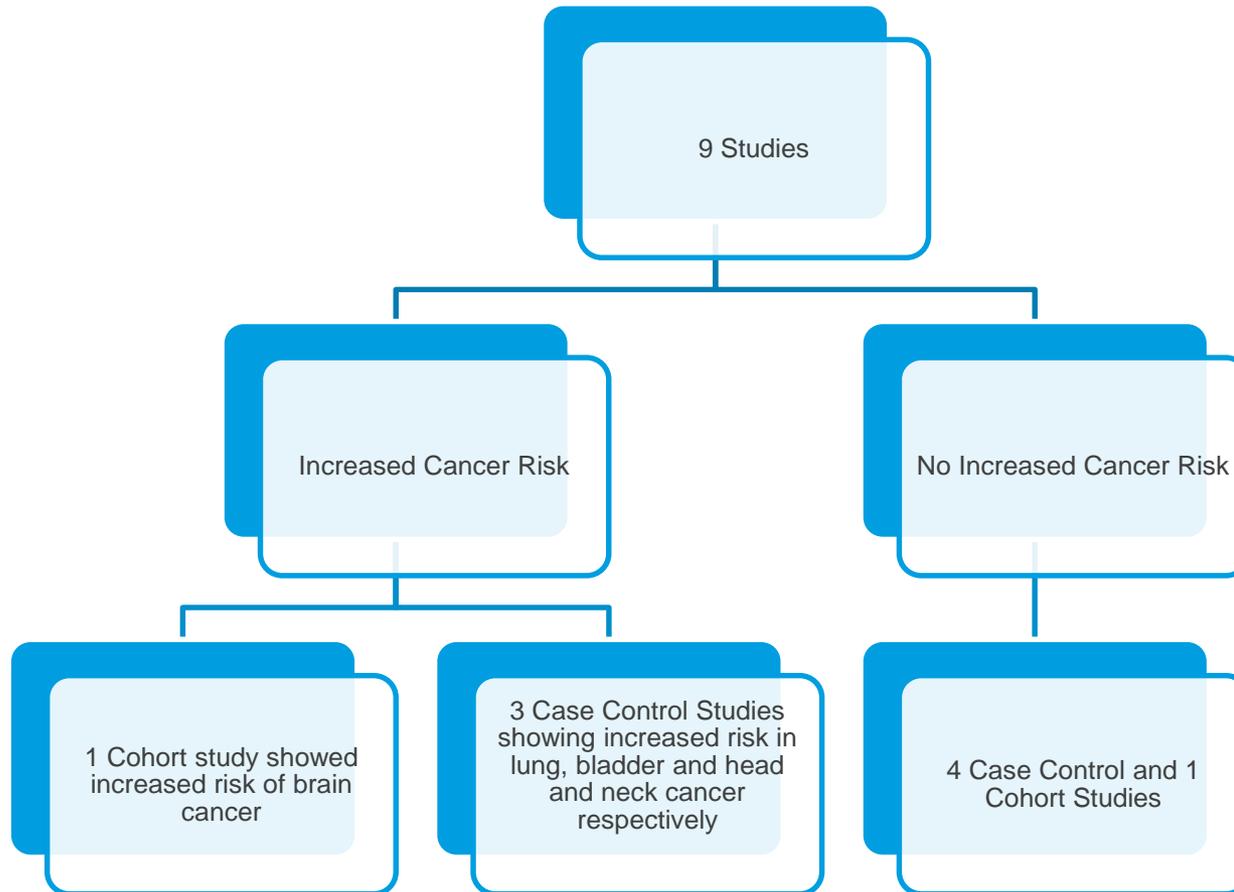
# Association of Marijuana with Motor Vehicle Crashes

Odds Ratio for Increased Crash Risk by Study and Indicator of Use



# Does Marijuana Use Increase the Risk Of Death?

## Marijuana and Cancer

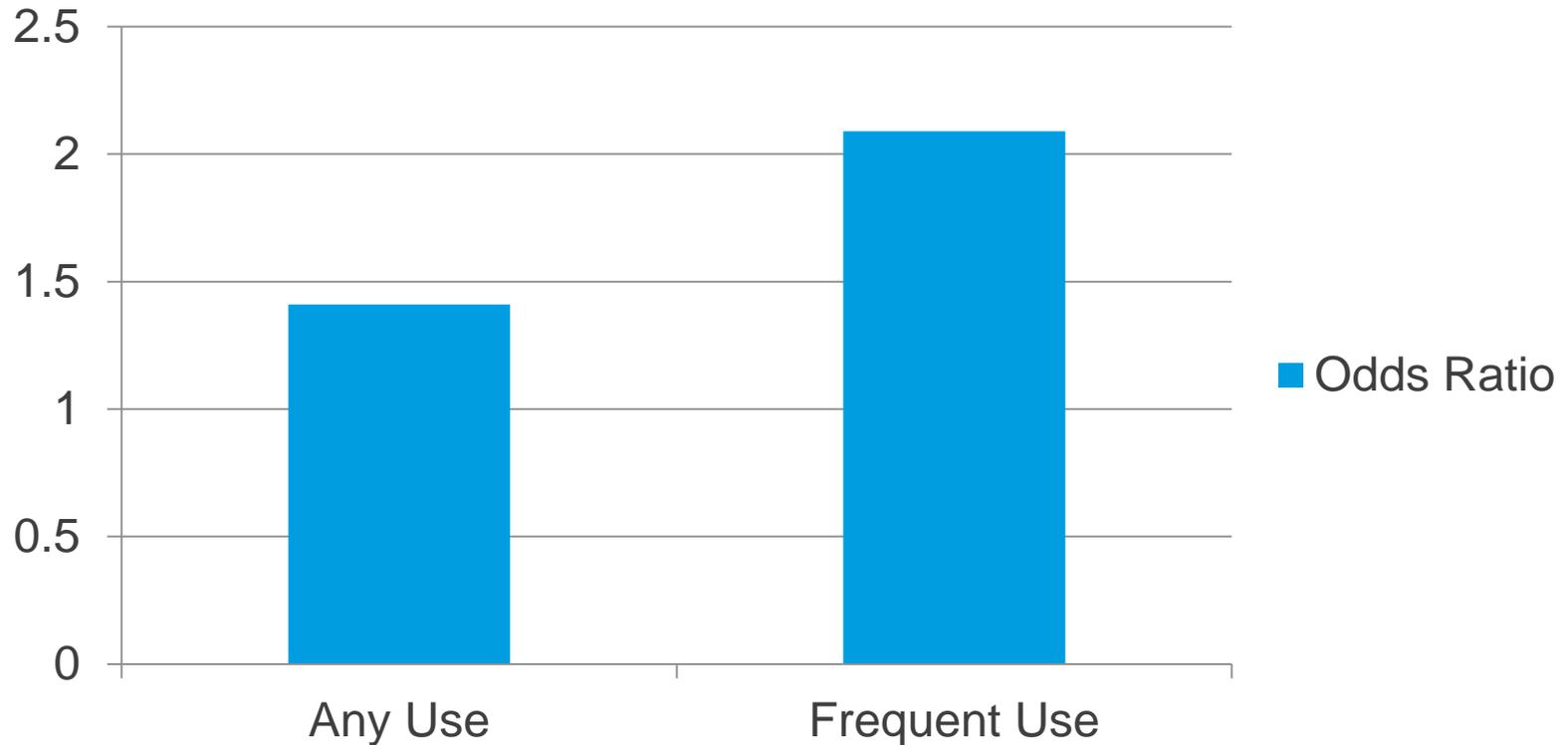


# Marijuana and Psychosis: Cause, Consequence or Correlation?

- ▶ Nearly 2000 studies since 1962 on this topic
- ▶ Several longitudinal population-based studies show:
  - Twofold increase in the risk of psychosis with regular marijuana use
- ▶ Vast majority of marijuana users do not develop psychotic disorders
- ▶ Heavy cannabis use may mean that young people who are vulnerable to psychosis develop the disorder when they may not have otherwise done so.
  - Certain polymorphisms of the gene encoding AKT1 potentially conferring risk of psychosis following smoking cannabis acutely
- ▶ Schizophrenia has been suggested to be a “hypercannabinoid” condition → high levels of Anandamide in CSF of these patients

# Risk of Psychosis with Marijuana Usage

## Odds Ratio by Amount of Usage



Bostwick JM, Mayo Clin Proc, 2012; 87:172-186.

# Marijuana, Anxiety and Depression

- ▶ Epidemiological evidence exists to support an association between regular Marijuana use and the development of anxiety and depression
- ▶ Evidence more mixed and less consistent compared to the association between Marijuana use and psychosis
- ▶ Depression and anxiety not only associated with Marijuana use but also predictive of individuals that will transition from use to addiction
- ▶ 2016 Prospective study of ± 35000 participants found association between Marijuana use and other substance use disorders but not other psychiatric disorders after adjustment

# Marijuana and ADHD

- ▶ Compared to the general population non-addicted frequent users where more likely to have an externalizing disorder such as ADHD which predated the start of the Marijuana use
  - Comorbid ADHD is a risk factor for frequent use

# Marijuana Use and Lung Function

- ▶ 2012 Longitudinal study (CARDIA) of 5000+ men and women followed over 20 years
- ▶ Occasional and low cumulative marijuana use was not associated with adverse effects on pulmonary function

# Marijuana Use and Lung Cancer

- ▶ Systematic Review 2016 of 19 studies
- ▶ Studies that examined lung cancer risk factors or premalignant changes in the lung showed an association with Marijuana use with regards to:
  - Increased tar exposure
  - Alveolar macrophage
  - Increased oxidative stress
  - Bronchial mucosal histopathologic abnormalities
- ▶ Observational studies of subjects with marijuana exposure failed to demonstrate significant associations between marijuana smoking and lung cancer after adjusting for tobacco use

# Medical Uses of Marijuana – 5 Major Conditions

## Severe nausea and vomiting

- Cancer chemotherapy and other conditions

## Weight loss and cachexia

- Cancer, HIV disease, other conditions

## Spasticity associated with neurologic disease

- Multiple sclerosis, Parkinson's disease, spinal cord injuries

## Pain syndromes

- Neuropathic pain, migraines, musculoskeletal disorders

## Glaucoma

# Issues with Medical Marijuana

- ▶ Many laws are vague re what conditions are appropriately treated with marijuana
- ▶ Many states only require a prescription
  - No ongoing relationship with a physician
- ▶ Most users smoke the “medication”
  - Only 2 oral meds are available for use for nausea and vomiting - Dronabinol & Nabilone
- ▶ Users prefer plant derived marijuana as onset earlier, easier to titrate
  - Only medication available in which the specific dose cannot be measured, no standardization of purity
- ▶ Novice users find the psychoactive effects of THC difficult to tolerate

# Issues with Medical Marijuana

- ▶ Most current users of medical marijuana were previous heavy, regular recreational users
- ▶ Example – study from California on applicants for use of medical marijuana
  - 90% had tried the drug before age 20
  - 90% had admitted daily or near daily use prior to application
  - 85% had tried other illegal drugs
- ▶ Four fold increase in the use of cocaine and methamphetamine in pain patients using marijuana

# Marijuana and Opioid Use

- ▶ Marijuana users are more likely to abuse or misuse opioids
- ▶ More likely to use other illicit drugs
- ▶ More likely to be involved with diversion of opioids
- ▶ Clearly has significant adverse effects on driving
  - Considered an absolute contraindication to operating a motor vehicle
- ▶ Marijuana Use Disorder with use of opioids increases the risk of overdose mortality

## Underwriting Medical Marijuana

Most medical conditions for which it is used are largely high risk condition

Ideally under regular care and supervision of a physician

- If not – more like recreational use

No indication or suspicion of misuse or abuse, history of withdrawal symptoms

Use in individuals under age 18 is very high risk

# Underwriting Medical Marijuana

Subtitle

Caution in individuals with any significant psychiatric illness, now or in past

Beware evidence of alcohol or other substance abuse currently or in the past

Current regular use of opioids is a red flag

Be alert to any significant driving criticism

High risk with certain medical conditions

- COPD, CAD, poorly controlled asthma, history of tobacco related cancers

# Underwriting Recreational Marijuana

- ▶ With the changing medico-legal landscape the distinction between medical and recreational likely to become less relevant
- ▶ Attitudes towards liberalization are normalizing especially in young people
  - Increased marijuana use disclosure
- ▶ Underwriters must be able to detect Marijuana Problem Use and Marijuana Use Disorder

# Current state of addiction terminology

- **Unhealthy Drug Use** - umbrella term for spectrum of drug use
- **Risky Use** is defined by the consumption amount likely to cause health problems
- **Problem Use** is defined as use that has resulted in **consequences** (health or other) but not yet diagnosable disorder
- **Substance Use Disorder** incorporates diagnosable substance disorders and range from mild (previously called substance abuse) to moderate/severe (aka substance dependence)

# Addiction Concepts

## DSM 5: Substance Use Disorder

- ▶ DSM-5 diagnostic criteria — DSM-5 diagnostic criteria for SUD are described below

A problematic pattern of use leading to clinically significant impairment or distress is manifested by two or more of the following within a 12-month period:

1. Often taken in larger amounts or over a longer period than was intended.
2. A persistent desire or unsuccessful efforts to cut down or control use.
3. A great deal of time is spent in activities necessary to obtain, use, or recover from the substance's effects.
4. Craving or a strong desire or urge to use the substance.
5. Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by its effects.
7. Important social, occupational, or recreational activities are given up or reduced because of use.
8. Recurrent use in situations in which it is physically hazardous.
9. Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance.
11. Withdrawal.

# Addiction Concepts

## DSM 5: Substance Use Disorder

- ▶ DSM-5 severity specifiers mild, moderate, and severe are based on the number of diagnostic criteria met by the patient at the time of diagnosis:
  - Mild – Two to three criteria
  - Moderate – Four to five criteria
  - Severe – Six or more criteria
  
- ▶ Substance abuse – Mild subtype of SUD
  
- ▶ Substance dependence – Moderate to severe subtype of SUD

# Marijuana and Addiction

- ▶ Prevalence of use peaks in late teens and early 20's then decreases significantly
- ▶ Lifetime dependence risk of 9%

## Compare to:

Lifetime Dependence Risks (Data from 2 papers)		
Nicotine	32%	67.5%
Heroin	23%	-
Cocaine	17%	20.9%
Alcohol	15%	22.7%

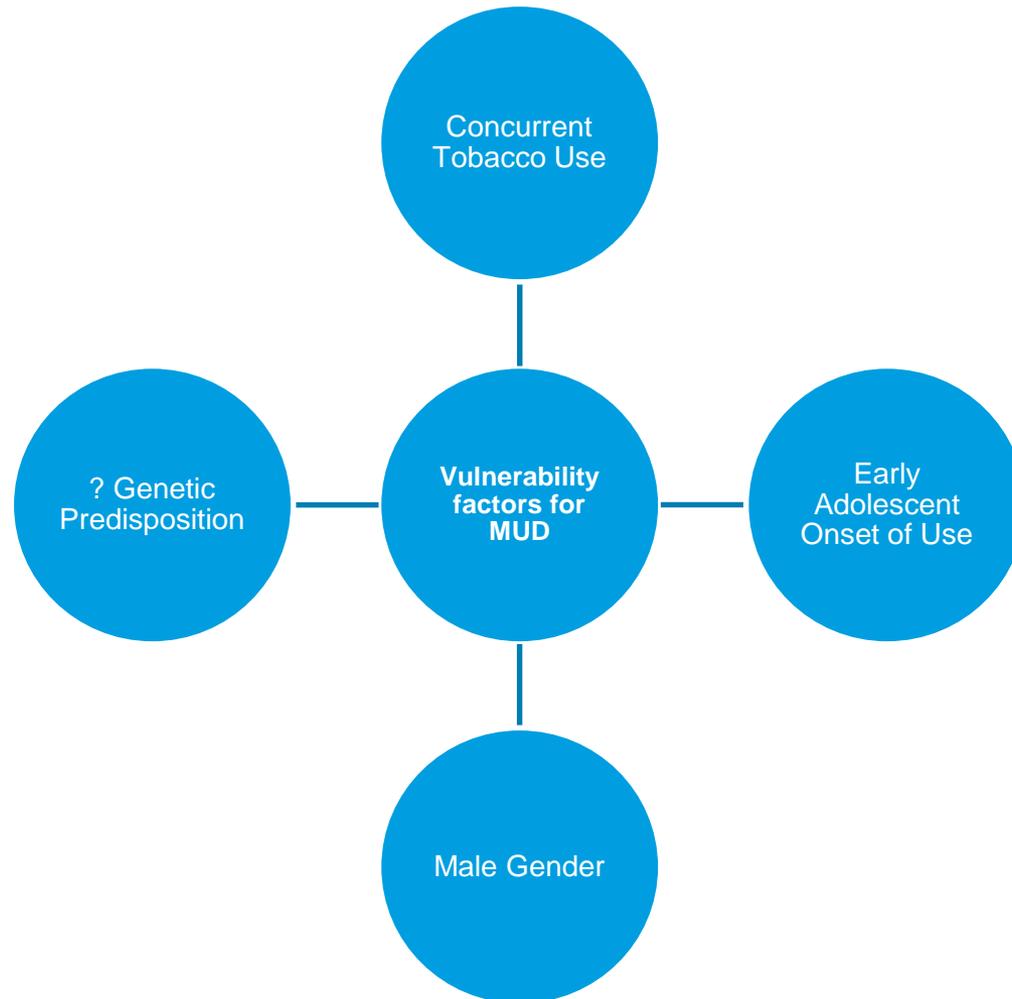
# Marijuana and Addiction

- ▶ Marijuana dependence develops insidiously
- ▶ Starts early (age 18 compared to age 20 for cocaine)
- ▶ Risk for new onset dependence is essentially zero after age 25

## Compared to:

- ▶ Cocaine → dependence risk continues until age 45
- ▶ Alcohol → users can keep transitioning from social use to dependence for decades after 1<sup>st</sup> use

# Marijuana and Addiction



# Marijuana and Addiction

- ▶ Marijuana exerts its influence through the Midbrain Reward Center → triggers dopamine release in the prefrontal cortex
  
- ▶ A withdrawal syndrome does exist
  - Irritability
  - Anxiety
  - Anorexia & weight loss
  - Restlessness & disturbed sleep
  - Craving
  
- ▶ Although much focus in regard to Marijuana is on the relationship with psychosis, Marijuana addiction is a much more common problem (a user of Marijuana is 9 times more likely to develop Marijuana addiction than develop psychosis)

# Marijuana and Early Use

- ▶ Adolescent brain particularly vulnerable to effects of Marijuana as it undergoes significant cerebral reorganization in particular the frontal lobes → Implicated in behavior
- ▶ Endogenous cannabinoid system plays a significant role in neurodevelopmental and maturational processes which includes synaptic pruning and white matter development → adding exogenous cannabinoids disrupts this development
- ▶ Adolescent use increases risk abuse and dependence of other illicit drugs
- ▶ Adolescent use is associated with an increased risk of developing anxiety and depressive disorders later in life
  - Weekly use → OR of 1.9
  - Daily use → OR of 5.6

## Final Thoughts on Marijuana Use

- ▶ Marijuana use has been documented for thousands of years with its users choosing it for social and psychological and medical rewards
- ▶ As it is a complex drug its use can come with a penalty ranging from mild cognitive impairment to disabling psychiatric disorders
- ▶ Future research should be more balanced looking at perceived benefits as well as adverse effects
- ▶ A significant gap in evidence base: *Still not sure what level of use of what type of cannabis is non-problematic*
- ▶ Also need to understand more about how variants of the drug produce differential effects — new synthetic cannabis as well as new forms of administration (for example, through vaping or edible forms)

# Final Thoughts on Marijuana

- ▶ Given the human body's widespread endocannabinoid signaling system pharmaceutical application does seem inevitable
  
- ▶ Potential pharmaceutical applications include:
  - Analgesics, muscle relaxants and anti-inflammatories
  - Appetite modulators
  - Antidepressants
  - Antiemetics
  - Bronchodilators
  - Neuroleptics
  - Antineoplastics
  
- ▶ Objective of pharmaceutical application should be:
  - Pure pharmaceuticals taken orally to bypass the health consequences of smoke exposure with the aim of modulating the endocannabinoid tone while keeping side effects at bay

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Questions?