MARIJUANA / CBD – FACT OR FICTION

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Talk for the Appalachian Addiction & Prescription Drug Abuse Conference
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("Natural" Marijuana had < 2% THC in the 1980s)

Disclosures

I have no relationship with any pharmaceutical company, or any part of the alcohol, tobacco or marijuana industries

Problem # 1

• Advocates for the legalization of medical and retail marijuana – are quick to point out all possible benefits – money, jobs, medical benefits
• But they use the words "cannabis" or "marijuana" for everything
• We must be clear what they are talking about
These are all “cannabis” but have very different effects on the mind/body

- **Hemp** – “green” plant with multiple uses (variety of Cannabis sativa plant < 0.3% THC)
- **CBD** – the non-psychoactive component – medicinal benefits – perhaps even low dose THC has medicinal benefits - but more research needed
- **High Potency THC** – the psychoactive component that is much higher concentration than what was available in the past

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The Cannabis Basics

- There are 3 basic plant types – all are from the “cannabis sativa” plant
  - **Cannabis indica**
  - **Cannabis sativa**
  - **Cannabis ruderalis**

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33 States and the District of Columbia have legalized Medical Marijuana, Even Though:

There is a dearth of rigorous research on the effects of marijuana for the most common conditions for which it is recommended
Colorado Medical Marijuana Registry

<table>
<thead>
<tr>
<th>Condition</th>
<th># of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cachexia</td>
<td>1,129</td>
<td>1.3%</td>
</tr>
<tr>
<td>Cancer</td>
<td>4,489</td>
<td>5.17%</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>1,133</td>
<td>1.3%</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>0</td>
<td>0%</td>
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<tr>
<td>Muscle Spasms</td>
<td>29,676</td>
<td>34.18%</td>
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<tr>
<td>Seizures</td>
<td>3,002</td>
<td>3.46%</td>
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<tr>
<td>Severe Pain</td>
<td>80,741</td>
<td>92.99%</td>
</tr>
<tr>
<td>Severe Nausea</td>
<td>14,068</td>
<td>16.2%</td>
</tr>
<tr>
<td>PTSD</td>
<td>8,000</td>
<td>9.21%</td>
</tr>
</tbody>
</table>


- 104 studies (n=9,958 participants)
- 47 RCTs, 57 observational studies
  - 48 – neuropathic pain, 7 – fibromyalgia, 1 – RA, 13 – MS, 6 – visceral pain, 29 – mixed or undefined CNCP
- Across RCTs – pooled event rates for 30% reduction in pain
  - 29.0% for cannabinoids vs 25.9% for placebo
  - NNTB – 24   NNTH – 6
- For 50% reduction in pain
  - 18.2% for cannabinoids vs 14.4% for placebo - ns
- Pooled change in pain intensity - equivalent to 3 mm reduction on a 100mm visual analog scale
  - "Unlikely that cannabinoids are highly effective medicines for CNCP"

Cannabis

- Complex alkaloid mixture of more than 400 compounds
- At least 60 different compounds described with activity on the cannabinergic system in the body
- Most abundant cannabinoids are
  - Delta-9 tetrahydrocannabinol (most psychoactive) - THC
  - Cannabidiol - CBD
  - Cannabinol
- Effect first discovered in 1963 by Raphael Mechoulam in Israel – he injected THC into aggressive rhesus monkeys – they became calm and sedated
Cannabinergic system

- Two main cannabis receptors
  - CB1—present throughout CNS
    - Hippocampus
    - Cortex
    - Olfactory areas
    - Basal ganglia
    - Cerebellum
    - Spinal cord
  - CB2 — located peripherally, linked with immune system
    - Spleen
    - Macrophages

Anandamides discovered in 1992 – Sanskrit word for “supreme joy”

Cannabis Ruderalis

- CBD
  - The newest craze on the market.
  - This is not intoxicating but can be psychoactive
  - There are some anti-inflammatory properties and it does cross the blood brain barrier
  - Hemp — is cannabis sativa, rudderalis, with a limited concentration of THC <0.3% THC
  - Products made from hemp seeds are virtually inactive.
  - HOWEVER, there is THC in virtually all CBD products
  - Bottom line – if you are at risk for being tested for drugs—don’t use CBD products

CBD cures?

- Arthritis? MS?
- Cancer? Migraines?
- Eczema? Schizophrenia?
- Obesity? Female sexual health?
- Mood?
- Memory?
- Huntington’s disease? Temperature?
- Alzheimer’s???????? Motor Control?
- Anxiety? Hunger?
- Bipolar?
- PTSD?
- Seizures: Epidiolex - now available as FDA approved
There is evidence that CBD can be helpful in some forms of epilepsy

- RCT of pharmaceutical grade CBD demonstrated low grade evidence of a positive effect but patients more likely to drop out due to side effects than with placebo
- Studies on dispensary cannabis – no RCTs, small N’s and serious to critical risk of bias – therefore felt to be insufficient evidence to recommend this

A medicine needs to be proven safe and effective and should come from a pharmacy

- Researchers at UC Davis studied medical marijuana from 20 dispensaries and found that they contained multiple fungal and bacterial contaminants that are highly toxic
- They warned that smoking, vaping or inhaling aerosolized marijuana is a real health risk, especially for those with chronic conditions in which patients are immunocompromised

CBD

- Virtually no single agency follows or regulates the end products of CBD.
- MED – denies responsibility because it is “CBD”
- FDA – has recently issued warning statements about the false claims but has yet to significantly enforce them, so….
- We have CBD at almost every store in America - with NO regulations on content and no supervision/regulation on who purchases this product.
- American Veterinary Medical Society does not recommend and yet there are dog products for purchase everywhere. THC is toxic to dogs.
CBD research

- Animal studies – great deal of variability and divergent results
  - Some evidence suggests CBD may have anxiolytic properties
  - Other evidence suggests in may have anxiogenic properties
- One recent study of single dose CBD given prior to fear conditioning in mice showed increased level of freezing during fear conditioning suggesting that CBD treatment increased the expression of generalized fear and the memory in CBD treated animals was more resistant to extinction. This suggests that CBD could be anxiogenic and counter productive in treating PTSD.
  - Uhernik AL et al. Learning and memory is modulated by cannabidiol when administered during trace fear conditioning. Neurobiology of Learning and Memory 2018;149:68-76

Some Evidence that CBD may protect against the adverse psychological effects of THC

- The activation of CB receptors by endocannabinoids inhibits excessive neurotransmitter release.
- THC mimics the effects of endocannabinoids but is not rapidly broken down and works broadly not locally
- CBD weakly binds to CB receptors and is capable of antagonizing effects of THC
- Not clear what THC/CBD ratio is optimum and what minimum concentration of CBD is needed to be “protective” – very high doses used in studies vs that smoked in a joint.

CBD Side effects

- CBD is metabolized via the liver - thought to be an inhibitor of CYP 3A4 and CYP 2D6
- There are a tremendous amount of drug interactions
  - Some of the most important medications altered by CBD
    - Anti-coagulants – Warfarin
    - Anti HIV medications
    - Seizure medications
    - Anti-rejection medications
- CBD can be liver toxic – in the Epidiolex trials- 5-20% developed elevated liver enzymes
Why Does This Matter?

- The public believes marijuana legally obtained from a licensed dispensary consists of pure, natural, cannabis that is safe and effective for a myriad of medical conditions.
- Medical, and now recreational, marijuana, both with high potency THC have been made available to the public without any scientific due diligence regarding its safety or efficacy.
- There is no legitimate research that indicates smoking cannabis with THC>10% is good for anything medically.

The Biggest Problem:
THC Content is Not Like It Used to Be…

- 1980 THC content was less than 2%
- 1997-4.5%
- 2006-8.5%
- 2015-20% or more
- Average potency of marijuana flowers/buds in Colorado is now 17.1% THC while the average potency for concentrates is 62.1%. Potency rates of up to 95% have been recorded. Smartcolorado.org
- After the Dutch observed negative impacts from rising THC potencies, a team of health experts concluded that THC potencies above 15% should be considered a hard drug.

The Most Popular Plant Strains

**Strain** | **THC content** | **CBD content**
---|---|---
Blue Dream | 17-24% | 0.1-0.2%
Sour Diesel | 19-25% | 0.1-0.3%
Girl Scout Cookie | 17-28% | 0.09-0.2%
Green Crack | 13-21% | 0-0.1%
OG Kush | 19-26% | 0-0.3%
Grand Daddy Purple | 17-23% | 0.1-0.1%

Comparing milligram doses

- A typical joint is 0.5 grams of marijuana
- If the THC % is 12 – 23% THC
- Then there is 60 – 115 mg of THC per joint
- Compare this to a medicinal form of Marijuana Sativex – oral mucosal spray
- It has 2.7 mg THC and 2.5 mg CBD per dose

Formulations

- Joint
- Oil
- Bong
- Dabbing
Edibles

Dabs, wax and shatter

- These are THC concentrates
- Typically made as extracts from the cannabis sativa or indica plant using propane or butane

What's in a dab

- Dabs can be anywhere from 90 mg to 250 mg typically.
- Internet has videos of people consuming a several GRAM dab
- One 90 mg dab is equivalent to 45 Woodstock joints
MARIJUANA Concentrates

“Bubbles”
“Rosin”

99% pure THC

THCa crystalline
100% pure
$120 per gram

Colorado Pediatric Marijuana Exposures in Children 9 and younger
Wang GS et al. JAMA Pediatr. 2016;170(9)

Colorado Pediatric Marijuana Exposures vs US Pediatric Exposures
Wang GS et al. JAMA Pediatr. 2016;170(9)
Medical and Retail Marijuana
Single Universal Symbol Examples

On Packaging/Labeling for all types of Medical and Retail Marijuana:

- Contains Marijuana. Keep away from children.

On Edible Medical Marijuana-Infused Product and Retail Marijuana Product:

- Medical Marijuana-Infused Product: The universal symbol must be printed or applied to the inner package compartment.

- Retail Marijuana Products: The universal symbol must be printed or applied to the outer compartment. The universal symbol must be printed or applied to the outer compartment at least once on each retail package containing retail marijuana products. The universal symbol must be printed or applied to the outer compartment at least once on the initial inner compartment of retail marijuana products.

Required for retail marijuana by January 1, 2019; medical marijuana, July 1, 2019.

2016-2017 National Survey on Drug Use and Health: Ages 12 and Older

Part Year Marijuana Use by Age-Grouping and Race, 2016-17
Following legalization use rates went up

Marijuana Use in the Past Month in Colorado, by Age Group

Marijuana Use in the Past Month in Kansas, by Age Group

Source: SAMHSA National Survey on Drug Use and Health: State Estimates

<table>
<thead>
<tr>
<th>Age Group</th>
<th>8th Graders</th>
<th>12th Graders</th>
</tr>
</thead>
<tbody>
<tr>
<td>8th Grade</td>
<td>Past Year Use</td>
<td>12th Grade</td>
</tr>
<tr>
<td>Marijuana</td>
<td>7.6%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Opioids</td>
<td>2.1%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>74.2%</td>
<td>32.7%</td>
</tr>
</tbody>
</table>

Top Drugs among 8th and 12th Graders, Past Year Use

*Only 12th graders current about alcohol use.
Consequences of Long-term or Heavy Marijuana Use Beginning in Adolescence

- Increased risk of Addiction
- Altered Brain Development
- Poor Educational Outcome with Increased Likelihood of Dropping Out
- Permanent Cognitive Impairment with Lower IQ
- Diminished Life Satisfaction
- Chronic Bronchitis
- Increased Risk of Psychosis Disorders, Especially in Persons with Genetic Predisposition.


The higher the potency of the drug the more potential for addiction

- Nicotine – FDA now talking about reducing nicotine concentration in tobacco
- Alcohol – 3.2 beer versus Vodka
- Cocaine – coca leaf versus crack cocaine
- Opioids – codeine versus Oxycontin
- Cannabis – marijuana of the 60s-80s when THC was <2% versus current high potency THC 17-28% in the flower, 85-90% in the concentrates

Addiction

Also referred to as Marijuana Use Disorder
- 9% of those who experiment with marijuana will become addicted
- 17% of those who start using as teenagers will become addicted
- 25-50% of those who are daily users will become addicted

Data from NEJM, Adverse Health Effects of Marijuana Use. Nora Volkow. June 5th 2014
Changes in cannabis potency and first-time admissions to drug treatment: a 16-year study in the Netherlands
Freeman TP et al. Psychological Medicine 2018

Fig. 1. Mean (95% CI) concentrations of 6-9-tetrahydrocannabinol (THC) in domestic herbal cannabis and number of first-time cannabis admissions to specialist drug treatment (per 100 000 inhabitants) from 2000 to 2015.

MJ Withdrawal Syndrome

- Increased anger
- Irritability
- Depression
- Restlessness
- Headache
- Loss of appetite
- Insomnia
- Severe cravings for marijuana
Hippocampus and Neurogenesis
All drugs of abuse negatively affect the hippocampus, decrease neurogenesis and impair the ability to learn new things - this is true for alcohol, cocaine, methamphetamines, heroin, nicotine, THC.

Learning tests

Exercise improves learning
Normal Brain Development during Adolescence - Neurotransmitter Development

- Lots of Dopamine and Glutamate - stimulatory neurotransmitters – “stepping on the gas” – go, go, go – learn, explore, do
- Decreased Serotonin and GABA – suppressive neurotransmitters – “stepping on the brake” located in the prefrontal motor cortex – the last part of the brain to fully develop


Behavioral Factors Relating to Substance Abuse in Adolescents

- ↑ neurobiological based tendencies for risk-taking with decreased suppressive and regulatory control
- lots of Go, go, go
- very little ability to put on the brakes
- ↓ in parental monitoring
- ↑ in peer affiliation

Endocannabinoid Receptors

- Are all over the brain – receptors for anandamides - “supreme joy”
- CB1 receptors regulate the balance between excitatory and inhibitory neuronal activity
- Exposure to cannabis during adolescence disrupts glutamate which plays an important role in synaptic pruning in PFC – disrupting normal brain development

IQ and Brain Development Studies

- Prospective study New Zealand – 1,037 individuals followed for 20 years
- Neuropsych testing at 13 before initiation of cannabis and again at age 38
- IQ decrease by 8 points with early persistent teen use of cannabis

IQ and Brain Development Studies

- Prospective study of 648 children and exposure to cannabis in-utero
- Women interviewed about the amount and frequency of marijuana use at 4 and 7 months of pregnancy and delivery
- Children assessed with IQ test at age 6
- Examiners blinded to exposure
- In Utero exposure (light to moderate marijuana users, approx. 3x/week) has a significant negative effect on school-age intellectual development
Recommendations From Cannabis Dispensaries About First-Trimester Cannabis Use
Dickson B et al. Obstet Gynecol 2018;131:1031–8
- Phone script - caller stated she was 8 weeks pregnant and experiencing morning sickness - "Are there any products that are recommended for morning sickness?"
- 400 dispensaries contacted in Colorado
- Nearly 70% of Colorado cannabis dispensaries contacted recommended cannabis products to treat nausea in the first trimester.
- Few dispensaries encouraged discussion with a health care provider without prompting.
- Example: "Technically, with you being pregnant, I do not think you are supposed to be consuming that, but if I were to suggest something, I suggest something high in THC."
- Bud Tenders Practicing Medicine without a License

What Does it Mean to Have a Decreased IQ?
- First, loss of 8 points will bring an average (50%) IQ of 100 down to the 29%.
- Less likely to get the “ideal” job
- Less likely to get a good score on SAT
- Decreased overall satisfaction in life
- Less likely to go to college
- Less likely to get married
- Less likely to stay married

Longitudinal influence of alcohol and marijuana use on academic performance in college students
Meda SA et al. PLOS ONE | DOI:10.1371/journal.pone.0172213 March 8, 2017
- Study from Yale University – tracked 1,142 students at two unnamed colleges
- Students achieved similar SAT scores
- Those with minimal alcohol and minimal cannabis use had average GPA of 3.10
- Those who drank alcohol without marijuana - average GPA of 3.03
- Those who used both alcohol and marijuana – average GPA of 2.66
- Not enough students used marijuana alone to evaluate
Marijuana and Mental Illness

- 3,239 Australian young adults were followed from birth to the age of 21.
- Potential confounding factors were prospectively measured when the child was born and at 14 years.
- After controlling for confounding factors, those who started using cannabis before age 15 years and used it frequently at 21 years were more likely to report symptoms of anxiety and depression in early adulthood than those who did not use cannabis. (odds ratio 3.4; 95% CI 1.9-6.1).
- Independent of individual and family background or other drug use.

Majority of visits with cannabis get a behavioral health evaluation

Number ED/UC visits with cannabis associated ICD codes or positive urine drug screens by adolescents aged ≥13 and < 21 by year to a tertiary care children’s hospital system in Colorado by year.


Marijuana and Depression

Bahorik AL et al. J Affect Disord March 15, 2017

- Participants were 307 patients with depression assessed at baseline, 3- and 6-months on symptoms, functioning and marijuana use – 40.7% used marijuana within 30 days of start.
- Marijuana use was associated with poor recovery.
- Those aged 50+ (B=0.44, p<.001) increased their marijuana use compared to the youngest age group.
- Marijuana use worsened depression (B=1.24, p<.001) and anxiety (B=0.80, p=.025) symptoms.
- Marijuana use led to poorer mental health (B=-2.03, p=.010) functioning (study from UCSF Department of Psychiatry).
Risk of Psychosis
- Using cannabis at a young age (<15-18) increases the risk of developing a psychotic disorder
- Risk is dose dependent and increases with greater frequency of use and with higher potency THC

High Potency Cannabis associated with a tripled risk for Psychosis
- London – analyzed 780 people ages 18-65, 410 with first episode psychosis and 370 healthy controls
- High potency – THC > 15% - 3X increased risk of psychosis
- Daily use – 5X increased risk
- Psychosis not associated with Hash < 5% THC

Attempts to add PTSD
- A growing number of states have identified PTSD as an approved condition for medical marijuana
- Observational study of 2276 Veterans treated in VA PTSD treatment programs
  - Never used marijuana – significantly lower symptom severity 4 months later
  - “Starters” – highest levels of violent behavior and PTSD symptoms 4 months after treatment
  - “Stoppers” – lowest level of PTSD symptoms at 4 months after treatment
Why Marijuana (THC) is not the answer for PTSD

- Similar as to why benzodiazepines are not the answer
- Temporary relief – numbing, disconnecting from the traumatic emotions
- Cognitive impairment, a-motivational syndrome, potential for psychosis or worsening psychosis from PTSD
- Addiction potential and vicious cycle
- False memories

False Memories

- Working and declarative memory deficits result from marijuana use and are thought to normalize with abstinence
- However, cannabis users have an increase susceptibility to memory distortions even when abstinent and drug free – compromising reality monitoring
- Riba et al. Telling true from false: cannabis users show increased susceptibility to false memories. Molecular Psychiatry 2015;20:772-777.

Cannabis and False Memories

- 16 heavy cannabis users (daily for last 2 years – average 21 years (3-39)
- 16 matched cannabis naïve controls
- Cannabis users abstained from cannabis use for 4 weeks prior to the study
- Memory paradigm included a study phase and a testing phase with participant in MRI scanner – 20 lists of 4 words
Marijuana and Suicide

- Multiple studies have documented a relationship between cannabis use and suicidality — Buckner et al. Psych Res 2017;253:256-259 — tested the utility of the interpersonal-psychological theory of suicide
- Large longitudinal study in Australia and New Zealand of over 2000 adolescents and maximum frequency of marijuana use found almost 7X increase in suicide attempts in daily marijuana users compared with non-users — Silins E et al. The Lancet psychiatry Vol 1 September 2014

Correlation of Marijuana and Suicide

In fact, veteran suicides have not decreased. Instead, they are up 32% since 2001, compared to a national increase of 23% during the same period — Congressional Hearing 4/27/17

Christine Miller, PhD
Cannabis use disorder and suicide attempts in Iraq/Afghanistan-era veterans

Kimbrel NA et al. J Psychiatric Research 2017:89;1-5

3333 veterans in cross-sectional, multi-site study by VA

Cannabis use disorder was significantly associated with both current suicidal ideation (p<.0001) and lifetime history of suicide attempts (p<.0001) compared to veterans with no lifetime history of cannabis use disorder.

The significance difference continued even after adjusting for sex, PTSD, depression, alcohol use disorder, non-cannabis drug use disorder, history of childhood sexual abuse and combat exposure.

Suicide is the number one cause of death in Colorado for individuals between the ages of 10 and 24

Children’s Hospital Colorado has seen the number of patients who have attempted suicide soar 600 percent since 2009.
Statistically significant 77.5% increase in the proportion of suicide victims with toxicology positive for marijuana (an absolute difference of 5.5%) for which toxicology data was reported (Chi square 77.2, p<0.0001). 2004-2009 compared with 2010-2015.

Suicide and Adolescent Cannabis Use

- Systematic review and meta-analysis
- Eleven studies, N=23,317 adolescents
- Risk of depression OR = 1.4
- Suicidal Ideation OR = 1.5
- Suicide attempt OR = 3.5
- Significantly higher in adolescent cannabis users than in non-users

Persistency of cannabis use predicts violence following acute psychiatric discharge

- 1,136 recently discharged psychiatric patients followed at 4 10-week time intervals and evaluated for marijuana, alcohol and cocaine use as well as episodes of violence (1992-1995)
- Persistency of cannabis use was associated with an increased risk of subsequent violence, significantly more so than with alcohol or cocaine
- Dugre et al. Frontiers in Psychiatry 2017;8:176

Cannabis use is a significant risk factor for violent behavior in early phase psychosis

- 265 patients with early psychosis followed prospectively for 36 months – dichotomized based on presence or absence of violent behavior
- Cannabis use disorder was the strongest risk factor of violent behavior
- CUD in 61% of patients with VB, 23% in those with no CUD
- Age of onset of cannabis use – 15 in violent patients vs 17 in non-violent patients
- Cannabis use linked to impulsivity and lack of insight
- Moulin V et al. Frontiers in Psychiatry 2018

Example of Premature (and in my opinion irresponsible) Reporting


2014 was also time when PDMP registration was mandated

"Legal marijuana is saving lives in Colorado, study finds" – report in Washington Post 10/16/17
Cannabis use and risk of prescription opioid use disorder in the United States

- 2001-2002 NESARC (wave 1) survey – 81% response
- 2004-2005 (wave 2) survey – 70.2% response rate
- N=34,653
- Compared cannabis use at wave 1 to prescription opioid use disorder at wave 2
- Cannabis use at wave 1 was associated with a significant increase in the odds of having a prescription opioid use disorder at wave 2
Solutions/Recommendations

- Educate, educate, educate, increase prevention efforts
- “Medical” MJ should come from pharmacies and go through FDA testing as all Rx drugs
- Limit THC concentrations to <10%
- Increase funding and availability of treatment
- Increase research on CBD and lower doses of THC
- Strong ban on any advertising that appears to be directed toward youth – for all drugs including marijuana, tobacco and alcohol

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