PROBLEMS WITH OUR HIGH POTENCY THC MARIJUANA FROM THE PERSPECTIVE OF AN ADDICTION PSYCHIATRIST

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("Natural" Marijuana had < 2% THC in the 1980s)

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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

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Popular Pla	ant Strains	
The Most Popular Plant Strains accessed on www.leafly.com – July 15, 2017		
THC content	CBD content	
17-24%	0.1-0.2%	
19-25%	0.1-0.3%	
17-28%	0.09-0.2%	
13-21%	0-0.1%	
19-26%	0-0.3%	
17-23%	0.1-0.1%	
	THC content 17-24% 19-25% 17-28% 13-21% 19-26% 17-23%	



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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

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- Increased anger
- Irritability
- Depression
- Restlessness
- Headache
- Loss of appetite
- Insomnia
- Severe cravings for marijuana

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Learning from drug use

- Dopamine is a salience factor that signals the brain that this is a "good" behavior to learn and remember
- Communication between the nucleus acumbens, amygdala, hippocampus and prefrontal motor cortex via glutamate begin to "hard wire" the behavior
- · However, not everyone becomes "addicted"

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Why Do They Become Addicted?

- Rewarding properties of addictive drugs in the "reward pathway" – higher potency releases more dopamine
- Genetic factors decrease in D2 receptors
- Prior sensitization by nicotine or other drugs as a child/adolescent
- Prior sensitization by stress/trauma/abuse

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RECOVERY OF BRAIN FUNCTION WITH PROLONGED ABSTINENCE





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All drugs of abuse negatively effect the Hippocampus, decrease neurogenesis and impair the ability to learn new things - this is true for alcohol, cocaine, methamphetamines, heroin, nicotine, THC



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Drugs and Learning

time, they can't find the platform

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Making the <u>Choice</u> to Use

- Exposure as a child can prime the brain and is a risk factor- but this doesn't have to result in addiction
- Addiction occurs when the person makes the choice to use – engaging the prefrontal motor cortex allowing the drug to "hijack" the brain

 The person can be addicted from the first use and the behavior is then "hard wired" in the brain



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suppressive neurotransmitters – "stepping on the brake" located in the prefrontal motor cortex – the last part of the brain to fully develop Schepis et al. Neurobiological Processes in Adolescent Addictive

Disorders. Am J Addictions. 2008;17:6-23

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↑ in peer affiliation

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- Acetylcholine ACH
- Another important brain neurotransmitter helps us focus and concentrate
- ACH innervation of the PFC reaches mature levels during adolescence – receptors = nACHRs
- Involved in promoting or preventing neuronal cell death – depending on developmental stage
- Nicotine works on these receptors and can mess up the fine tuning of the brain during adolescence





Endocannabinoid Receptors



- 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** <u>disrupting</u> <u>normal brain development</u>
- Lubman et al. Cannabis and adolescent brain development. Pharmacology and Therapeutics 2015;148:1-16

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Grey Matter Volume Differences Associated with Extremely Low Levels of Cannabis Use in Adolescence

- 46 boys and girls with just one or two incidences of cannabis use versus controls with no exposure to cannabis matched on alcohol, nicotine use high school students in 4 European Countries
- · Also studied controls who went on to use cannabis 2 years later versus those who didn't
- Significantly greater GMV in those who used cannabis in bilateral hippocampus, amygdala, striatum, extending into the left prefrontal cortex
- There was no GMV differences in THC naïve 14-year-olds who later used cannabis at 16, so differences did not precede use and were not explained by group differences in demographic, personality, psychopathology, or other substance use factors The endocannabinoid system (ECS) mediates maturation-related neural reorganization which may place adolescents at heightened vulnerability to structural brain effects of cannabis surgoung on endocements on time of ranid neural meturation
- exposure as adolescence is a time of rapid neural maturation

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- · 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
- · Goldschmidt L et al. J Am Acad Child Adolesc Psychiatry, 2008.



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

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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

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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
- $^\circ$ 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
- Hayatbakhsh MR et al. Cannabis and anxiety and depression in young adults: a large prospective study. J Am Acad Child Adolesc Psychiatry 2007 Mar;46(3):408-17.

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



Wang GS, Davies SD, Haimo LS, Sass A, Mistry KD. Impact of marijuana legalization in Colorado on adolescent emergency and urgent care visits. Journal of Adolescent Health 2018 Available online 30 March 2018.

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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,
- 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
- Pierre JM Risks of increasingly potent Cannabis: the joint effects of potency and frequency. *Current Psychiatry* 2017;16:14-20

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High Potency Cannabis associated with a tripled risk for Psychosis

- DiForti et al. Lancet Psychiatry, 2015
- 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

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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
- Wilkinson et al. J Clin Psychology 2015

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

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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

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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
- $^\circ$ 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

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 interpersonalpsychological 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

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Cannabis use disorder and suicide attempts in Iraq/Afghanistan-era veterans

Kimbrel NA et al. J Psychiatric Research 2017:89;1-5 3233 veterans in cross-sectional, multisite 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



Lifetime Cannabis Use Disorder

The significance difference continued even after adjusting for sex, PTSD, depression, alcohol use disorder, noncannabis 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.

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- 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

Gobbi G et al. Associations of cannabis use in adolescence and risk of depression , anxiety, and suicidality in young adulthood: a systematic review and meta-analysis. JAMA Psychiatry. 2019;76:426-434.



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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
- · Olfson M et al. Am J Psychiatry 2018;175:47-53







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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
- $\ensuremath{\cdot}$ 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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