Cannabis Use Disorder: a much underappreciated addiction

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I WANT YOU TO TURN OFF YOUR CELL PHONE
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Part II: Marijuana Addiction
Cannabis Use Disorder

Figure 3) Percent of Americans with a Substance Use Disorder by drug of choice

- Alcohol: 64.5%
- Prescription Opioids: 7.5%
- Marijuana: 15.7%
- Cocaine: 4.1%
- Tranquilizers: 2.3%
- Heroin: 1.7%
- Hallucinogens: 1.2%
- Stimulants: 1.9%
- Inhalants: 0.6%
- Sedatives: 0.5%

NSDUH 2012
MARIJUANA ADDICTION
Cannabis Use Disorder

- 9-10% of users will meet diagnostic criteria for cannabis use disorder
- Cannabis is the most commonly identified substance used by those admitted to substance abuse treatment facilities in 2013
- 335,833 (18.4%) of those treated for addiction problems in 2010 list marijuana as their primary drug of choice TEDS, N-SSATS 2012
Addiction: About 9% of Pot users may become dependent, 1 in 6 who start in adolescence and 25-50% of daily users

American Psychiatric Association’s Diagnostic Manual (DSM) has included marijuana use disorders since 1980. DSM-5 added Marijuana Withdrawal as a diagnosis.

* Nonmedical Use *Source: Anthony JC et al., 1994
Addiction Is A Developmental Disease that starts in adolescence and childhood

Age at tobacco, alcohol, and cannabis dependence per DSM IV


Adolescent Pot User 2-4 X more likely to go on to other drug problems
The Earlier Teens Use Any Substance, the Greater the Risk of Addiction

Percent of Population 12 & Older with a Substance Use Disorder

- 28.1% First Used Before 15
- 18.6% First Used 15 to 17
- 7.4% First Used 18 to 20
- 4.3% First Used 21+

Source: CASA analysis of the National Household Survey on Drug Use and Health (NSDUH), 2009.

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Medical Marijuana States Have Higher Youth Marijuana Use Rates

Two independent, peer-reviewed studies looking at medical marijuana states in the 2000s concluded that:

States with medical marijuana programs had an increase in marijuana use not seen in other states.

Substance Abuse and Mental Health Services Administration (SAMHSA), State Estimates from the 2008-2009 National Surveys on Drug Use and Health, 2011
The Developing Adolescent Brain

Teen Brain is at Increased:
Risk of damage from drug and alcohol use
Risk of developing addiction and social problems
Risk of Mental Illness
Desire for risk taking and exposure to harm

Brain is not yet wired to control impulses and emotions to form good decisions
Cannabis Use Disorder

- 12-18 yr old users are 3-7 x as likely to have CUD than 22-26 yr old users

- CUD is 2 x as likely in states with medical marijuana (2.6%)

- Patients with mental illness are 3 x as likely to have CUD

RD Schwartz-Bloom, 2011
States that Legalized Marijuana Use For Medical Purposes Have Significantly Higher Rates Of Marijuana Use and of Marijuana Abuse and Dependence

NESARC: National Epidemiologic Survey on Alcohol and Related Conditions
Cannabis-Related Disorders
Tolerance, Dependence, Withdrawal


- Cannabis Use Disorder
- Cannabis Intoxication
- Cannabis Withdrawal
- Other Cannabis-induced Disorders
- Unspecified Cannabis-Related Disorders
Cannabis Use Disorder
Diagnostic Criteria DSM-5

1. larger amounts and longer than intended
2. Inability to decrease or control use
3. Excessive time to get, use, and recover
4. Cravings or urge to use
5. Failure to fulfill work, school, home roles
6. Continued despite negative consequences
7. Important activities ceased or reduced
8. Continued in physically hazardous situations
Diagnostic Criteria Continued

9. Continued despite physical/psychological problems

10. Tolerance: \( \uparrow \) amount needed to get desired effects or decreased effects from same amount of cannabis consumed

11. Occurrence of withdrawal or use to relieve or avoid withdrawal

Mild = 2-3 of symptoms of criteria
Moderate = 4-5
Severe = 6 or more
Marijuana Tolerance

• Rapid development to most marijuana effects

• Some Cross Tolerance to alcohol but not with other drugs of abuse
Tissue Dependence

• Seen with daily use of 2-3 “joints” over several weeks (500mg ave. X 15% = 75 mg.
• Classic loss of control, compulsive use, cravings and continued use despite development of negative consequences
• Abstinence induces physical withdrawal syndrome
• Cross Dependence unclear but use often occurs in combination with nicotine, alcohol and other addictive substances
Marijuana Withdrawal Syndrome

Symptoms occur within 8 hours of abstinence but can be delayed up to 72 hours. Usually peak in severity on day 10 and may last for up to 45 days or longer.

Symptoms consist of: irritability, anger, anxiety, restlessness, nightmares/sleep disturbances (REM rebound), headaches, depressed mood, craving, decreased appetite, sweating, chills, pain, mild tremors (“cold dog shakes”)
Cannabis Withdrawal DSM-5

Within ~a week after cessation: 3 or more of the following after a few months of heavy use:

1. Irritability, anger, or aggression
2. Nervousness or anxiety
3. Sleep difficulties (insomnia, disturbing dreams - REM rebound from suppression)
4. Decreased appetite or weight loss
5. Restlessness
6. Depressed Mood
7. Plus at least one of the following physical symptoms causing significant discomfort:
• Abdominal Pain
• Shakiness/Tremors (“cold dog shakes”)
• Sweating
• Fever
• Chills
• Or Headaches

Most Signs and Symptoms 1 - 7 last for 1 to 2 weeks, Sleep Disturbances can last for more than 30 days.
Historic Evolution of Addiction Science
Dr. James Olds, McGill University
Toronto, Canada 1954
Operant Conditioning

Dr. Terry Robinson
U of Mchg. 2004
Incentive Sensitization Research Confirmation
Dr. Robert Heath,
Tulane University, 1959
ADDICTION DEFINITION
American Society of Addiction Medicine

- is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

– (ASAM definition, Short Version)
Addiction Pathway
Brain Circuits & Processes

- **Reward/Reinforcement (Go)**

  *I prefer Survival/Reinforcement*

  Hyperactivity then Hypoactivity

- **Control (Stop)**

  Impaired, dysfunctional or disconnection of Go and Stop

Bill Cohen: Overactive go, Damaged Stop & Lack of Communication between them
Neurons in Earth’s Fossil Record: Spinal Cord to Diencephalon to Mammalian-Meso Cortex to Neo Cortex

Fish 500 mya
Reptiles 300 mya
Amphibians 315 mya
Mammals 220 mya
Primates 65 mya
Hominids 5 mya

Earth 4.5 Billion Years, Life from 4 Billion Years
CNS Addiction Pathway

Control Circuit

Survival/Reinforcement Circuit
Brains Addiction Pathway

Stop Switch
- Prefrontal cortex

Go Switch
- Nucleus accumbens
- Lateral hypothalamus
- Amygdala
- Hippocampus
- Substantia nigra
- Ventral tegmental area
Location of the nucleus accumbens in human CNS

Blum K. et al. (2014)
Brain on Cocaine

Minutes after shooting or smoking

Courtesy of Nora Volkow, Ph.D.
THC in Marijuana Mimics Brain’s Anandamide
All Addictive Substance Involve Dopamine Activity
Natural and Drug Reinforcers
Increase Dopamine in NAc

Drugs of abuse increase DA in the Nucleus Accumbens, which is believed to trigger the neuroadaptions that result in addiction.

Di Chiara et al., 1997
Di Chiara et al., 1997
Control Circuitry = Stop Switch

- Orbital Prefrontal Cortex – Especially left ventral medial OFC
- Fasciculus Retroflexus (anterior)
- Lateral Habenula (posterior and mesocortex terminal)
Last Area of Brain to Develop is Prefrontal Cortex

- Functional at age 25!
- Fully Developed At age 40+

Reasoning, Impulse Control, Temporal Processing, Planning, Judgment
Prefrontal Cortex of the Neocortex

- Carries out Executive Functions, Judgment
- Attention, Planning, Reasoning, Decision Making, temporal processing
- Impulse Control (Adaptive vs. Non-Adaptive Behavior)
- Abstract Thinking
- Memory, Voluntary Motor Control

At age 13-14 (8th Grade) inability to suppress Non-Adaptive-Behaviors predict future drug use problems  
Norman et al. J. Drug and Alc. Depn. 2011
Brain Reward Pathways

Prefrontal Cortex

Nucleus Accumbens

Arcuate Nucleus

Ventral Tegmental Area

Dopamine

Glutamate

Opioid Peptides

Courtesy of Dr. John Hart, Portland, Oregon
Single Photon Emission Computed Tomography (SPECT) Scan

Normal Brain

Marijuana Abuse

Courtesy of Daniel Amen, M.D.
New Research Concerns Regarding Pot Use Especially with Increased THC%

- NIDA: 3.75% THC 1995 ↑ to 15% 2013
- Brain white matter development disruption in adolescents
- Brain scans of 100 16-17 year olds who used pot daily for at least 3 years in adolescence showed shrinkage of their thalamus, globus pallidus and striatum to those who didn’t
- These findings are projected to correlate with memory, cognition problems, ↓ IQ by 8 points & 1gpa and implies pot quickened or induced schizophrenia. Healthy subjects scored 37 times higher on memory tests!
Chronic Marijuana Use: No Link to later physical or health issues


**Major Defects of Study:**
*Issues were self-reported, subjects not asked if they had medical evaluations*
*Life Outcomes or Problems were not measured*
*Later Onset Health Problems could not be assessed in the younger subject population*
*Pot Users studied, no control population included*
*Study initiated in 1987 so less potent pot and subjects were not heavy or daily users*
*46% of study data is missing from the report*
*Large 27.7% Concussion rate not discussed*

Madras, B K (2015), *Marijuana Report*
Diathesis-Stress Model of Addiction & Related Disorders

- HEREDITY – Type I
- ENVIRONMENTAL – Type II
  Stress (esp. Trauma) & Poor Nutrition
- PSYCHOACTIVE DRUG TOXICITY – Type III

Note: each phenotype has to have elements of the others to be activated
Type I: Heredity


Most Project 40 - 60% Contribution to Addiction
Genetic Variations

DNA is the “Cookbook”
89 genes associated & > 900 suspected

- CREB
- CHRM$_2$
- CHRNA$_4$
- GABRA$_2$
- Leu-Pro allele
- NQD$_2$
- ADH$_4$
- KMALDH$_1$
- COMTmet158met
- DRD$_2$A$_1$ Allele
- Tipsy Gene: CYP2E1
- AUTS$_2$
- GABRG$_3$
- 3p26-3p25
- TAS$^2$R16
- SNCA
- OPRK$_1$
- PDYN
- CYP$_2$D$_6$
- CHRNA$_4$
- DeltaFosB
- Novelty Gene: DRD$_4$
- Finnish Rage/Alcohol Gene: HTR2B

2010 NIDA Genome Wide Association Study (GWAS)
Compared to a control brain (top), neuroscientist James Fallon’s brain (bottom) shows significantly decreased activity in areas of the frontal & temporal lobe linked to empathy and morality—anatomical patterns that have been linked with psychopathic behavior.
Type II: Environment: Stress & Nutrition

Type III: Toxicology: Neurochemical & Neurofunctional Allostasis
Type II: Environment

- Early Childhood Trauma (physical, sexual, emotional abuse, tragic event, grief, anything that is traumatic to an individual)
- Stress including Mental Health Disorders
- Nutritional Deprivation and Imbalances

All recently associated with epigenetic changes resulting in different expression of dominant and recessive traits or turning on or off of genes
Epigenetic Expression

Methylation, Acetylation, Phosphorylation of genetic peptide and 5hmC tags result in altered expression of genes
Identical Twin Mice with Divergent Epigenetic Expression

Transfer RNA = “Recipe”
Micro RNA = the “Chef”
Even Identical Twin with Epigenetic Expression of Different Races
Chang and Eng Bunker
Conjoined Identical Twins born 1811
Type III: Neurotransmitters
Homeostasis/Allostasis

Tolerance, Tissue Dependence, 
up/down regulation, enzyme 
induction, auto receptors, drug 
dispositional, pharmacodynamics, 
altered transporter mechanisms, 
epigenetic expressions, et al.
Psychoactive Drugs Affect Perception, Mood, and States of Consciousness by mimicking or Disrupting the Natural Chemistry of the Brain

Expanded Definition = Any Behaviors (e.g. Gambling) that Alter Moods and Affect the Brain’s Addiction Circuitries and Pathways
Taking one: *Uptown, Downtown and “Outatown”*

- **CNS Stimulants** increase the electrical and chemical activity of the brain (caffeine to ‘Ice’)
- **CNS Depressants** decrease the electrical and chemical activity of the brain (‘booze’ to ‘benzos’ to opioids)
- **All Arounder**s (Psychedelics) distort and interfere with brain perceptions to produce delusions, illusion, hallucinations, & synesthesia (DXM: ‘Robo’ to ‘paka-lolo’ to Sylvia d)
- **Misc:** Inhalants, Anabolic Rhoids, Behaviors
Hereditary hater of alcohol
Hereditary lover of alcohol
Alcoholic mouse

DBA/2j = Genetic alcohol/Drug avoiding mice

C57bl/6j = Genetic alcohol/drug loving mice
Hereditary hater of alcohol
DBA/2J

Hereditary lover of alcohol
C57bL/6J

Alcoholic mouse

[Equations with images of mice and alcohol glasses]
Cannabinoid CB₁ Receptors in Human Brain are Lower in Marijuana Abusers

Van Loere et al., 2007. Hirvonen et al., Mol Psychiatry 2012
High Novelty Seekers have Low CB₁ Receptors (CBR)

Van Laere, K et al. 2009
Marijuana use lowers CB₁ Receptors: CB₁ receptors are high in those who are low novelty-seeking or extravagance needy – low for those who are high in novelty-seeking or extravagance needy have low CB₁ receptors.

K Van Laer et al., 2009

But, Receptors recovery with abstinence

j. Hirvonen et al. (2012)
Why Can’t Addicts Just Quit?

Non-Addicted Brain

Control

Saliency → Drive

Memory

Addicted Brain

Control

Saliency → Drive

Memory

Because Addiction Changes Brain Circuits

Adapted from Volkow et al., Neuropharmacology, 2004.
Substance-Related and Addictive Disorders

- Misconceptions, Misunderstandings, Myths & Stigma [weak, bad, stupid, crazy]
- 60% illicit drugs sold in suburbia or rural US
- 75% Hard-Core drug users: actively and even gainfully employed
- <5% Alcoholics fit “Wino” stereotype
- US lifetime prevalence = 30% (Inc. Mensa)
Brief Review of Addiction Treatment
TREATMENT CONTINUUM

- Detoxification
- Initial Abstinence
- Long-term Abstinence
- Recovery
Acute Reinforcing Effects
Courtesy of Dr. John Hart

Limbic Area
• Role: Drive Generation (SURVIVAL)
• Intervention: Pharmacotherapy

Prefrontal Cortex
• Role: Executive Function
• Intervention: Counseling
Clinical Interventions

• National Registry of Evidence-Based Program and Practices: SAMHSA & State
• Cognitive Behavioral Therapies: Motivational Interview/Enhancement, DBT coping skills, Contingency Management (CM) & relapse prevention tools
• Levels of Change
• Marijuana Anonymous or other 12-Step group involvement
Pharmacological Cue Extinction via naltrexone and acamprosate
Meds for Marijuana Addiction

Note: None FDA Approved so all are Off-Label

- kynurenic acid
- N-Acetylcysteine dietary supplement
- bupropion,
- buspirone
- divalproex,
- naltrexone,
- lithium,
- antidepressants, and
- THC replacement
Developing Medications: N-Acetylcysteine for Marijuana-Dependent Adolescents

Proportion of Negative Urine Cannabinoid Tests Over Time Among Cannabis-Dependent Adolescents

Challenges to Maintenance of Continued Abstinence

- Cognitive Impairment (30-80%)
- Endogenous Craving (Allostasis)
- Environmental Triggers or Cues
- Post Acute Withdrawal Symptoms (PAWS)
- Unaddressed Mental Health Issues
Addiction Recovery
Kibou is the Japanese Kanji (calligraphy) meaning hope. It is comprised of Ki = hope and Bou = wish. Combined it symbolizes a good sign to overcome difficult situations or failures.

Addiction is one of the most treatable and manageable of all chronic, persistent medical disorders with positive treatment outcomes that favorably compare with the treatment of diabetes, hypertension, asthma, et al. chronic, persistent illnesses.

Relapse is prevalent in the treatment of all chronic medical disorders. Relapse rates after addiction treatment also compare favorably with treatment of other illnesses.
RECOVERY
The Resilient Brain

8-10 Months Rigorous Uninterrupted Treatment for Reasonable Outcomes

Implies time needed for brain to become functional

Takes up to 2 years for greater functioning to return
Recovery

- Continued Abstinence
- Discovery of Natural Highs
- Recovery of neurotransmitters and of natural brain functions
- Positive lifestyles and quality of life enhancements
- Remember: Not an Event but a Process

One does not cure addiction, you treat it and manage it like any other chronic persistent medical disorder.
Recovery

• Continued Abstinence
• Discovery of Natural Highs
• Recovery of neurotransmitters and of natural brain functions: Homeostasis
• Positive lifestyles and quality of life enhancements
• Remember: Not an Event but a Process
Normal

Cocaine Abuser (10 da)

Cocaine Abuser (100 da)

Courtesy of Nora Volkow (Volkow, Hitzmann, Wong, et al 1992)
ADDICTION CAN BE TREATED

Partial Recovery of Brain Dopamine Transporters in Methamphetamine (METH) Abuser After Protracted Abstinence

Normal Control  METH Abuser (1 month detox)  METH Abuser (24 months detox)


Dopamine Transporter Binding (DAT) Recovery in Meth Addiction

DAT Recovery with prolonged abstinence from methamphetamine

Volkow et al. J. of Neuroscience 2001
Alcohol Brain Resilience

Intoxication

Sober: 30 days
7 years Methadone use

Deborah - Methadone 100 mg/day
Xanax 20 mg/day FOR 20 YEARS

ONLY SIX WEEKS FOLLOWING DETOX
Dr. Ken Blum’s patented: Synapta GenX, KB220Z

Neuronutrient complex “normalization” of caudate, accumbens and putamen regions of heroin addicts demonstrated by fMRI Scan
Treatment Works!

- 3 to 5 Yrs. Continued sobriety = 50% (1yr 80%)
- Decrease Crime = 75%
- $7-$12 Savings for every $1 Spent
- Positive results from 6-8 mo. Treatment
- Coerced treatment better than voluntary
- Decreased Psychiatric (40%), Family/Social (50-60%), Medical (15-20%), Employment Problems (15-20%)
- Culturally consistent better than generic treatments

Belenko, et al. 2005
Issues Involved with Marijuana Urine Drug Screen (UDS)
Urine Analysis (UA) Complications
from Rewood Toxicology Lab Information Sheet

- THC and its metabolites take 2-4 hours after smoking to be detectable in urine
- They can persist in levels above the usual 50 ng/ml cut-off concentrations for up to 30 days (lower levels up to 6 months detectable in brain tissues) but in general
- 1-3 days detectable from infrequent use
- 7-10 days regular use (several times/week)
- 30 days heavy/daily use (if 50 ng/ml, longer if lower cut-off)
ng/ml RIA Value to Use Pattern
from Redwood Toxicology Lab Information Sheet

• > 500 ng/ml = possible recent use or high dose use or chronic use
• 250-500 ng/ml = possible continued elimination in chronic user or recent high dose use in infrequent user
• < 250 ng/ml = Possible terminal elimination in chronic use or recent use in infrequent user
Second hand exposure controversy

Secondhand exposure controversy: 6 experienced user smoked in same room with 6 non users first 5.3% THC in a non ventilated room then 11.3% THC in a ventilated room. Immunoassays of 20, 50, 75, and 100 ng/mL cutoffs along with GC-MS. Only one + occurred at the 50 ng/mL cutoff but multiple +s occurred at 20 ng/mL. THCCOOH levels of GC-MS for the non-users ranged from 1.3 to 57.5 ng/mL. Results show that 20 ng/mL cutoffs will yield second hand positives with increased potency THC but for only a few hours post-exposure. Note that Oregon DPT has 20 ng/mL cut off and ave. THC ~15% in 2013 and increasing.

Urine Creatinine
from Rewood Toxicology Lab Information Sheet

- Creatinine in urine is related to muscle and gender with normal range of 40-300 mg/dl in males and 37-250 mg/dl in women
- <45 mg/dl is generally used to determine a dilute invalid urine sample (requires retest)
- SAMHSA set <20 or <2 mg/dl level as a definite dilute or substituted sample used to evade a urine test
THC/Creatinine Ratios

THC metabolites (i.e. carboxy-THC) concentration fluctuates with a person's fluid intake on a day by day basis.

Increased fluids lowers both THC and Creatinine concentration and decreased fluids increases both.

Calculation of THC/Creatinine Ratio can correct for this fluctuation to identify current use or sample diluting attempts.
THC/Creatinine Ratios
from Rewood Toxicology Lab Information Sheet

- THC value divided by creatinine value multiplied by 100 = the THC/Creatinine Ratio
- The ratio is compared to the ratios of other previous urine tests
- An increase ratio of more than 50% between two urine test ratios generally indicates recent renewed marijuana use
THC Urine Spiking?

Past alleged sequestration of metabolite carboxy-THC in fatty tissues which is released by exercise or metabolic effects to produce a THC spike in urine test result when none used.

Now dismissed by most analytical labs and claim that THC/Creatinine Ratio of <50% can differentiate this effect from use.
Marijuana has Positives and Negatives like all drugs

Marijuana is the most commonly used illicit drug in the U.S.

Marijuana use generally begins in adolescence

Use of marijuana can have a wide range of effects on an individual’s brain, body and behavior including short and long term effects on such functions as:

- Brain development
- Memory and cognition
- Motivational systems and reward
- Addiction
- Lung health

In recent years there has been an increase in both treatment admissions for marijuana abuse and in Emergency Department visits involving marijuana toxicity

BUT: Its molecules also have great potential medical benefits
A lot of information compressed in a very short time!

Questions?
Thank You!

PowerPoint available at: www.cnsproductions.com

Darryl Inaba, PharmD., CATC-V, CADC III
Lunch Break: Reality Bites!

Fantasy Vs. Reality!