Marijuana: New Findings, MH Concerns &CUD - Inconvenient Truths

Indiana Association for Addiction Professionals Virtual Conference 2020
Darryl S. Inaba, PharmD., CATC-V, CADC III
Addictions Recovery Center & CNS Productions, Inc.

Thank you, IAAP, for keeping safe by making this a virtual conference and thank all who tuned in for your heroic efforts to provide services to those struggling with addictive disorders.

Thank you, for your heroic efforts to provide essential services to those struggling with addictive disorders during this pandemic, please take care to be as safe and healthy as you can.

Substance-Related and Addictive Disorders In America Results in:
• More Deaths and More Hospitalizations than any other public health threat (Mortality/Morbidity)
• More Incarceration and Criminal Justice Interventions
• Once, Greater Financial Costs than all other Expenses (now more spent on COVID-19)

Yet, Addiction is the most treatable and preventable of chronic persistent medical disorders.
Current COVID-19 impact on US Health since March 5, 2020 as of 10/10/2020

• Confirmed infections 7,648,256
• Deaths – 213,390

COVID-19 Pandemic

Addiction in USA Endemic

Opioid OD deaths and Addictions
Surging in Pandemic

Annual U.S. Lives Lost to Addiction

LEGAL Drugs:
- Tobacco-Nicotine 480,000
- Beer/wine/Booze-Ethanol 130,000
- Rx Medications- opioids/benzos/etc. 38,000 so ~650,000 LD deaths

ALL ILLEGAL DRUGS COMBINED:
- Heroin, methamphetamine, cocaine, etc.
  -24,000, 2017 ~60,000 Op deaths

Consider: Civil War (4 yrs.) 750,000
  WWI (2 yrs.) 116,516
  WWII (5 yrs.) 405,399
  Vietnam (20 yrs.) 58,209

Addiction kills more people in 1 year than 27 years of WWI, WWII & Vietnam

Despite documented human use for thousands of years, what Marijuana is and what it does to the brain and body remains shrouded by strong biases that result in contradictory “scientific” studies and findings.

This session will strive to clarify the basics: Is it a drug and does its use have potential harm or benefits

Research is complicated and compromised by multitude of variables: Plant contains >480 biologically active substances, > 80 cannabinoids, THC has > 100 active metabolites administration methods create >2000 toxins, various growth processes/pesticides/nutrients. Research is compromised & difficult to control for consistent findings

Cannabis-Use Disorder, CUD
Treatment & Science of Addiction

Darryl S. Inaba, PharmD, CATC-V, CADC III
Director of Clinical and Behavioral Health Services, Addictions Recovery Center
Director of Research & Education, CNS Productions, Inc.
Marijuana is a Drug!

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Current Concerns:
- ↓ perception of any harm: lungs, driving, pregnancy
- ↑ use/abuse especially by youth
- Impact on developing adolescent brain
- Ever ↑ potency, issue of synthetics
- New data of associations: schizophrenia, ↓ IQ (8 pts. & 10PA), c. hyperemesis syndrome, seizures, Heart 4.8X, Testicular Cancer
- Cannabis Use Disorder: Addiction an underappreciated and inconvenient truth
- Tobacco/liquor industry legalization interest
- Lack of treatment/prevention resources

Recreational Use Legalization Concerns:
- Currently the #1 reason adolescents enter drug treatment programs; impairment of driving not vetted
- Great & increasing THC concentrations (3 to 4 times more than in 1970s pot); more health problems
- Tobacco and liquor industry support legalization (Philip Morris now owns pot domain names)
- Tobacco now trafficked illegally to avoid taxes
- Actual increased marijuana crimes with legalization
- Alcohol = 2.6 million arrests/year, marijuana 800,000
- Revenue??? for Education (Co) Health (Wa)
- What about prevention, interventions and treatment?  
  Kevin A. Sabet 11/2/12 UofF

In 2009 Illegal Drug Use Increase by 9%
U.S. marijuana, use in 2009 highest ~decade and continued to increase through 2014. methamphetamine, ecstasy (MDMA), Rx Drugs finally leveled off and decreased 2011
Perception of illicit drug use as harmful lowest in ~decade

Incidence & Perspective
(Johnson Monitoring the Future; DAWN; PATS, NSDUH et al.)
- 12-18 yo: 39% tried, 20% current, 3% daily
- 18-25 yo: 48% tried, 5% daily use of pot
- Other Drugs by US high school seniors:
  Alcohol: 88% tried, 5% heavy use
  Nicotine: 27% tried, 17% daily use
  Methamphetamine/cocaine: ~8% tried, <1%
  Ecstasy (MDMA): 10% tried, < 0.1 daily use

By 2010 Past Month Use of Marijuana by Teens > Cigarette use

Percentage of U.S. 12th-Grade Students Reporting Past Month Use of Cigarettes and Marijuana, 1977 to 2013

Current Pot Use Increased to 12.7% of 8th, 30% of 10th and 36.4% of 12th Graders in 2013 & 2014 Monitoring the Future Study
Percentage of U.S. 12th Grade Students Reporting Past Month Use of Alcohol, Cigarettes and Marijuana


Correlation of Perceived Risk and Marijuana abuse


Only 39.5% HS Seniors in 2013 view regular use & 16.4% in 2014 view occasional pot use as harmful & 6.5% use daily.

Monitoring the Future Survey 2014
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- 24,000

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**2014 Cole Memo: DoJ guidance for attorneys and law enforcement**

Prevent:
- Marijuana distribution to minors
- Sale revenues too criminals, gangs, cartels
- Diversion from legal to illegal states
- State authorized activities used to cover up other illegal drugs or activities
- Violence and firearms in cultivation and distribution of marijuana
- Drugged driving and adverse health consequence
- Growing on public lands & environmental dangers
- Possession or use on federal property

*[DoJ announced it will rescind this Memo on 1/4/18]*

**47 States and D.C with Medical Pot Laws**


2012 Meta Analysis of National Surveys:
- Residents of Med. Pot States have:
  - Higher rates of Pot Use
  - Higher rates of Pot abuse/dependence
  - Much Lower Adolescent Perception of Pot being Harmful and
  - Much Higher Adolescent Average Pot Use

As compare to States with no Med. Pot Laws  

**Only 3 states totally prohibit MJ 2020**

[Map of medical and recreational marijuana legalization by state]
**SAM Smart Approaches to Marijuana**

**Status Report on State Compliance of Federal Marijuana Enforcement Policy**

August 30, 2017

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**5-Years of Colorado Marijuana Legalization**

Marijuana Accountability Coalition 2018

- Youth & young adult ↑ use 65% since legal
- ↑ youth suicides
- ↑ African and Hispanic youth arrests
- ↑ alcohol consumption in the state
- Calls to poison control centers ↑ 210%
- ↑ marijuana related emergency room visits
- 844% ↑ in Post Office seizures
- ↑ crime rate: 11 X faster than US, 8.3% property crime and 18.6% violent crimes
- Positive UDT has doubled the national average
- ↑ DUID with 76% marijuana involved and 88% ↑ fatal traffic accident involvement

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**Lessons Learned: THC Adverse Impact on Health Outcomes 2018 & 2019**

- Mental Health Issues: psychosis, depression, anxiety, suicide, brain changes & addiction
- Lung and Cardiovascular: hypertension, MI, cardiomyopathy, arrhythmias, stroke and cardiac arrest
- Fetal Exposure: cognitive impairment, hyperactivity, impulsivity, inability to focus, increased risk of still births and autism

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**Lessons Learned: State of Oregon March 2018 & May 2019**

- OR. & AK 12-17 yo annual use lead U.S.
- OLCC inspection - ~25% sales to minors
- Underage Binge Drinking + pot ↑
- Pot ER visits in Central & Bend Or. ↑ steeply
- Burns from Dabbing on the rise, ↑ health cost beyond tax revenue
- 70% Or. pot sales are on the Black Market
- 50% DRE assessed drivers test + for THC

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**Lessons Learned from First States and Wa. DC Recreational Pot March & May 2019**

- 12-17 yo current use ↑ above Nat. Ave.
- Suicides testing THC + ↑
- Suspensions from HS for Pot ↑
- Marijuana-Related Driving Deaths ↑
- ↑ Pot-Related ER visits, Hospitalizations, Accidental Exposures, Poison Center Calls
- ↑ Crime (black market trade & property crimes)
- Pot-Related Crimes & Juvenile Offenses ↑
- ↑ Workplace Problems (Outages, Accidents)

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- Memory, Motor impairment, anxiety, agitation, paranoia and Psychosis
- Especially seen in youth along with ↓ IQ, ↓ academic performance, drop out, depression, psychotic disorders, suicide attempt, life satisfaction and addiction
- Pregnancy (now most common drug used during pregnancy) 50% ↑ in low birth weight
2018 Daily Marijuana Use by US Teens Remained Fairly Unchanged but was higher in States with Medical or Legal Pot Laws and Vaping Cannabis Increased Significantly

US Teens Vaping Marijuana first surveyed in 2017, Increased Significantly in 2018 Especially in States with Medical/Legal Pot Laws

Increasing Marijuana-Positive Fatal Crash Drivers in Colorado After Widespread Adoption of Medical Marijuana

Proportion Of Fatal Crash Drivers MJ-Positive in Colorado and 34 States Without Medical MJ, 1994-2011

Date of widespread Medical MJ implementation in Colorado (2009)

Salomonsen-Sautel S et al., Drug and Alcohol Dependence 2014.

Increased Fatal Auto Accidents

Similar trends

Colorado and Washington were the first states to legalize recreational marijuana. The states have seen a similar trend in the number of traffic fatalities in which a driver tests positive for marijuana.

Rocky Mtn. High Intensity Drug Trafficking Area

- 30% increase in THC drug test since 2013
- 93% inc. pot packages leaving Co. since 2010
- Increase ingestion of edibles by children
- Increase edible suicide and homicide reports
- Camel and Winston investment in vaping THC in e-cigarettes, pre-rolled joints sold like cigarettes
- Jan. $2M & Feb $3M tax revenue but projected $11.16M/mo or $134M/year, ~$7M in Aug.
- Increase youth use of edibles and vaporizers with increased poison-control calls
• Must be age 21 but marketed to youth with discounts with student ID cards
• No credit card rule but pot shops also sell e.g. gardening supplies
• No sales post 7 pm and limits on amount sold to out of staters openly violated (24 hr. solds)
• 10 mg. THC/serving on edibles but even one gummy bear has 4 servings, soda 10s/bottle
• Now 16.53% of fatal traffic accidents involve pot and arrests for using while driving increased 316%, requiring 90 new police Drug Recognition Experts to be trained.
• More than 200 lawsuits filed in Colorado regarding pot legalization, costs!

Oregon Measure 91 allows:
• 4 marijuana plants (1 to 10 lbs of pot each)
• 8 oz. of usable marijuana “420”, “Nugs”
• 1 oz. of hashish extract “710 gear” (Oregon butane hash/honey oil >90% THC
• 72 oz. liquid marijuana, 6 pk of 12 oz with each containing 10 servings/container
• 1 lb or 16 oz of edibles or marijuana products: candy, cookie, Cheeba Chews (in Co. each gummy bear has 4 servings)

47 States and D.C with Medical Pot Laws

2012 Meta Analysis of National Surveys:
Residents of Med. Pot States have:
• Higher rates of Pot Use
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Emergency Department Visits Involving Selected Drugs: 2008
Source: SAMHSA, 2008 DAWN
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

Odds Ratio

Past Year MJ Abuse/Dependence Past Year MJ Use Past Year MJ Abuse/Dependence Among Current Users

NESARC: National Epidemiologic Survey on Alcohol and Related Conditions

18-25 Year-Old Monthly Marijuana Use Legal vs. Non-Legal State Averages

Legalized states 48% increase in use (19.79 v 29.23)
Non-legalized states 10% increase in use (16.79 v 19.89)

10.79% 16.79% 19.79%
0.00% 5.00% 10.00% 15.00% 20.00% 25.00% 30.00% 35.00%
2005-2006 2015-2016
Non-legalized state averages
Legalized state averages

Rocky Mountain (Co) & Northwest HIDTA (Wa) Continual Monitoring of Recreational Pot 2014 on

• ↑ Driving after pot use, ↑THC DUI and ↑ Fatal THC Auto Accidents
• ↑ 12-17 yo use: Co now #1 & Wa #6 in US
• ↑ Elementary School Disciplinary Violations
• ↑ Poison Ctr. Calls, ↑pot poisonings especially in 0 – 5 yo children
• ↑ Drug Crimes and Homocides esp. in Denver, Co
• 2.5-fold ↑ in psychosis associated with pot use

Colorado fatal auto accidents with driver being THC positive

Number of Operators Involved in Fatal Accidents who Tested Positive for Marijuana

NHTSA
Marijuana Poisoning in young children has increased 150% in Colorado since legalized

Percentage of drivers high on pot during fatal accidents in Washington State more than doubled between 2013 and 2014
AAA Foundation for Traffic Safety (2016)

Surge increase of youth pot use and addiction in legal vs. non-legal states

Increase in CO. youth pot arrests since legalization
Also, age 12-17 first time marijuana use increased 65% since legalization in Colorado
D.C. marijuana arrests ~triple after legalization & disproportionately among African Americans

Smoking pot creates 2,000 more psychoactive and carcinogenetic chemicals

Growing and storing It can also result in exposing users To Insecticide, Fungicide, and Rodenticide or harmful fungus and bacteria

Pot intoxicated drivers in fatal traffic crashes increased 88% 2013-15

Major cannabinoids found in cannabis (Phytocannabinoids)

• Delta-9-tetrahydrocannabinol (Δ9-THC): most psychoactive, less therapeutic
• Cannabidiol (CBD): analgesia; antiseizure moderates effects of THC; healthiest
• Cannabinol (CBN): anticonvulsant
• Tetrahydrocannabinvarin (THCV): anti-inflammatory
• Cannabichromene (CBC): mixed effects
• Cannabicyclol (CBL): analgesic
• Plus 60 or so other cannabinoids

Marijuana “Pot”

3 Species & 7 taxa: near infinite #s of varieties, hybrids, & Strains with wide concentrations of some 480 chemicals, 66 are cannabinoids, ~80-100 of which are psychoactive (plus their metabolites >100 identified in human body) cannabinoids; Δ9-THC (tetrahydrocannabinol) are considered to be responsible for most effects

• Cannabis sativa
• Cannabis indica
• Cannabis ruderalis

Sinsemilla and growth manipulations

CLINICAL PHARMACOLOGY OF CANNABIS

• 95-99% plasma protein bound; lipophillic
• hydroxylation, oxidation, and conjugation for rapid clearance from plasma not from body
• First-pass metabolism (after PO admin.) to 11-OH-THC
• Elimination is slow: days to weeks 20-35% found in urine; 65-80% found in feces; stored in adipose;
• Pregnancy Category C: in breast milk
• Fast, good absorption if smoked or vaporized (20-37%)
• Slower if orally ingested; Local effects if liniment
3 species but infinite number of strains & hybrids

Marijuana Calendars with “buds” of the month

Average THC and CBD Levels in the US: 1960 - 2011

TETRAHYDROCANNABINOL

THC Content of Cannabis

More Potent Pot

Marijuana Potency Monitoring Project University of Mississippi

Average Potency of US street marijuana

• 1976 – 2% THC
• 1983 – 4% THC
• 2005 – 5.2% THC
• 2007 – 7.3% THC
• 2008 – 10.1% THC (project funding discontinued)
• 2015* - 11.04% THC; 17 & 21% Co. & Wa.

Informal reports as Potency Monitoring Project discontinued

THC Dosing: <7mg=Low dose, 7-18mg=Medium, >18mg=High Dose but more than 80 cannabinoids plus 400 phyto and 2,000 combustion bioactive molecules

Average THC and CBD levels in the US: 1960 - 2011

- THC
- CBD

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*Informal reports as Potency Monitoring Project discontinued
Origin of “420, 4/20, 42°” Street Code for Marijuana

- Hitler’s birthday: April 20, 1889
- Teatime in Holland
- 420 active molecules in pot
- Police code for marijuana abuse in progress
- SB420 California’s Medical Pot initiative
- Multiplier product of a Bob Dylan song #s
- The 5 ‘Waldos’ (they hung out at a certain wall) of San Rafael HS 1971. 4:20pm was meeting time on 4/20 during harvest season to go rustle someone’s pot patch

Marijuana Mechanism of Action

- 1964 Δ⁹-Tetrahydrocannabinol
  *Mechoulam, Raphael (1964)*

- 1988 Cannabinoid Brain Receptors: CB₁ & CB₂
  *Howlett, Allyn & Devane, William (1988)*

- 1992 Endocannabinoids: anandamide & 2AG now 4 others
  *Mechoulam, Raphael (1992)*

Brain Cells or Neurons

- Unusual shapes: Unipolar, bipolar, pyrimidal, purkinje, astrocyte, glial but all have “hair-like” projections
- More limited (less new ones) than other body cells
- Have no physical contact with each other
- Communicate via chemical messenger molecules that are made from the protein you eat

Dr. Inaba’s Belief: Holcomb’s Jewelry clock sign (corner of Haight-Ashbury) when I came to SF in 1966 and this photo taken by me on 12/28/17. It has been stuck on 4:20 forever!

Courtesy, Takeichi Laboratory, Nagoya, Japan
Psychoactive Drugs Mimic, Disrupt, or Block Neurotransmitters

SOME EXAMPLES -

UPPERS: Catecholamines (Norepinephrine, Epinephrine, Dopamine) + Serotonin and Acetylcholine

DOWNERS: Endorphin, Enkephalin, GABA, Serotonin

PSYCHEDELICS: Serotonin, Acetylcholine, Alpha Psychosin, Norepinephrine, Dopamine, Anandamide, 2AG
1990’s Endocannabinoids

- Specific Brain and Body Receptors: CB1 & CB2
- Neurotransmitter Anandamide or AEA for CB1 in brain and CB2 in peripheral NS
- 2AG (2-arachidonylglycerol) for both CB1 & CB2
- Noladin Ether or AGE primary CB1 & some CB2 activity
- Also NADA, CB1 Selective & OAE mainly CB2

The Brain’s Natural Marijuana: Endocannabinoids

Similarity of THC chemical structure to neurotransmitter anandamide

Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

- Brain Development
- Memory and Cognition
- Motivational Systems & Reward
- Appetite
- Immunological Function
- Reproduction
- Movement Coordination
- Pain Regulation & Analgesia
Cannabinoid lack receptors in spinal chord thus TI is ~114x less deadly than booze

But, how is risky or toxicity defined in this 2/23/15 report?

Marijuana use lowers CBR receptors: CBR 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 CBR receptors. K Van Laer et al., 2009. Also lower dopamine release in heavy cannabis users C. Van de Gaarse (2010). Mol. Psychiatry

Yellow = recovery of CBR

But, Receptors recovery with abstinence J. Marinacci et al. (2012)
Receptors are on Axon Terminal Buttons

THC or Endocannabinoids attach to CB1 Receptors and inhibit the release of neurotransmitters

Graham Johnson, 2004

Evolving Forms of Marijuana: Strains/Hybrids, Extract/Oils/Edibles, Synthetics, Vaping/Juicing

Synthetic Marijuana (THC) aka Synthetic Cannabinoids (SC) Analogs sold as Herbal Incense “Not For Human Consumption!”

$30 to $40 per 3-3.5 gm packets

“Designer Drugs” aka “Club Drugs”

• Modifications of existing molecules of abuse (isomers, analogs, isosteres, et al.), drugs laws specifically name a molecule and not the modifications of such

• Finding molecules with entirely different chemical structures that produce similar effects to illegal recreational molecules (Structure-Activity Relationship)
Example: prescription amyl nitrite and designer “poppers”

Amyl Nitrite

Isobutyl Nitrite

For Example: Designer Volatile Nitrites

Amyl Nitrite the Rx “Parent” Molecule

“Poppers, Snappers, Bananas”

Isobutyl Nitrite

Cyclohexyl Nitrite

Butyl Nitrite

Isopropyl Nitrite

Thus, almost any Alkyl Nitrite


Now 3 Types of Cannabinoids

• Endocannabinoids: 5 ligands, main ones - anandamide and 2-AG
• Phytocannabinoids (botanical): some 80-100 identified, tetrahydrocannabinol, cannabidiol, and cannabinoi are main ones
• Synthetic Cannabinoids (SC): 9 chemical families - Cannabinoids, naphthoylindoles, naphthylmethylindoles, naphthoylpyrroles, naphthylmethylindenes, phenylacetylindoles, cyclohexyphenols, aminoalkylindole.
• These can be 5 to 800 times more potent and have 6 -12 hrs duration of action

Evolving Forms of Marijuana: Strains/Hybrids, Extract/Oils/Edibles, Synthetics, Vaping/Juicing

2000’s Synthetic Cannabinoids

Herbal “Incense”

$K_{2}$, $K_{9}$, Spice Gold or Silver or Diamond, Budda Blend, Yucatan Fire, et al contain JWH-015, HU-210, WIN-55/212-2, CP-47/497/C6 or other THC agonist. By 2012 about 100 such molecules. These “designer pots” are anywhere from 5 to 800 times more potent than THC. UA test for JWH series in 10/10. Also THC Antagonist: rimonabant (Accompli)
Illegal 1st in 12 States, then in U.S. 2010
• Some of these synthetic cannabinoid products (eg K2 and Spice) are now illegal in 12 States (Ala, Ark, Geo, III, LA, Mbg, Miss, NJ, NY, OH, Tx) and many communities as well
• On 10/13/10 Oregon Board of Pharmacy adopted “Temporary Rule” classifying K2 and Spice as Schedule I Controlled Substance
• Federally 5 were banned in 2011 but many more are not covered by any bans

Synthetic Cannabinoids more Toxic than Phytocannabinoids
• Reports of anxiety, dry mouth, tolerance, increased HR, cardiac arrest, pulmonary & cerebral edema, increased blood pressure confusion, psychosis, paranoia, coma, seizures, kidney failure and even deaths. Cannabinoid Hyperemesis Syndrome
• Also contaminated with brodifacoum rat poison 2018
• Developing Drug Tests: JWH-018, -073, -019, -250 and for AM-2201 now ~12 available. Tests for others continue to be developed.
• Cost: $17.00 to $35.00 for the complete UDS screen of available standards

So, Now Legal Potpourri
And, Chill Spice: marketed as aromatherapy incense

Suspected to contain JWH-200, -250, and/or CP-47, -497

Also new oral pot street products
Marijuana Gel Caps: Pot + Olive Oil Blended and Capsulized

“Dabbing” butane hash oil (BHO) aka “wax, honey oil, budder, shatter”, et al.

Alleged to result in a waxy product containing 70-95% THC!
Many different extraction processes and devices (“710 Gear”)

New Cannabis Substances also produced with butane, nitrous oxide, alcohol, carbon dioxide and even cold water

“Ear Wax Weed, Butane Hash Oil (BHO), Cannabis Oil, Honey Oil, Shatter, Wax, Bubble Hash”, et al.
Extraction process is known as “Dabbing”

Juicing Medical Marijuana
No Heating, Non-Psychoactive?
**How do vaporizers work?**

- When cannabinoids are heated to between 285 °F (140 °C) and 392 °F (200 °C) they literally boil and vaporize.
- Studies show that vaporization is most effective at around 338 °F (170 °C)
- A vaporization temperature over 392 °F (200 °C) will burn the cannabis, creating unwanted smoke.
- But, note that most commercial vape pens are really aerosols not vaporizers.

**Also Commercial Products (e.g. PureGold) via Tetralabs CA. et al. sold as medical marijuana**

- Sold as liquid, gel cap, gel Ampoule and solution for E-Cigarette Use
- Alleged 95% cannabinoid with 75% Δ9-THC

**Use of E-cigarette devices to “vape” cannabis products: produces odorless vapor**

**CDC: 2,758 cases in 50 states/2 territory, 64 deaths of vaping-related many involving THC products by mid Feb. 4, 2020**

- linked to vitamin E acetate 11/8/19
- & more often in THC vape (Schuchat, A (2019))
- Also, flavored E-Cigarettes (esp. cinnamon) linked to Risk for Cardiovascular Disease

**Nicotine/Cannabis Vaping Lung Injury**

- four imaging patterns that correlated with pathological findings attributable to vaping, including acute eosinophilic pneumonia, diffuse alveolar damage, organizing pneumonia, and lipid pneumonia resulting in patterns of giant-cell interstitial pneumonia, hypersensitivity pneumonitis, and diffuse alveolar hemorrhage.

- Henry TS et al. (2019) NEJM

- flavored vapes found to contain: Vanillin, banned in tobacco produces as it produces Acetals that irritate the lungs & menthol that may react with other chemicals used to create toxins
- Erythropel HC, et al. (2019)
* Of 860 injured patients who provided information – 85% used THC products and only 10% used nicotine-only products CDC
* Condition now known as EVALI (e-cigarette or vaping product use-associated lung injury) CDC
* EVALI associated with use of Vitamine E Acetate Blount BC, et al. December 2019
* Synthetic THC sold in CBD Vape Oil Cartridge (Yolo®) out of Grants Pass Oregon sickens dozens Associated Press, September 2019

Pot Edibles Not Medibles Targeted for Adolescents and even Preadolescents
Pot-flavored candy takes a licking
Anti-drug forces angry over treats made with hemp oil

ATLANTA - Marijuana-flavored lollipops with names such as Pugge Kiss, Acapulco Gold and Katz are showing up on the shelves of convenience stores around the country, angering anti-drug advocates.

"It's nothing but dope candy, and that's nothing we need to be turning our children to," said Georgia state Sen. Vincent Fort, who has persuaded some convenience stores to stop selling the treats.

The confections are legal, because they are made with hemp oil, a common ingredient in health food, beauty supplies and other household products. The oil retains a marijuana's gravelly taste but not the high.

Feds Warn Of Marijuana-Filled Gumballs

Anti-drug forces angry over treats made with hemp oil
Medical Synthetic THC
2000’s Synthetic Cannabinoids

- dronabinol (Marinol)
- nabilone (Cesamet)
- THC + CBD (Sativex)
- Cannabinol Extract (Cannador)
- CBD ( Epidiolex) in IND-Phase III trials

Conclusion Part I: Despite growing acceptance and legalization, Important to remember that Marijuana is actually many drugs in a single substance

Marijuana, Memory, and the Hippocampus

High levels of CB1 receptors (orange and yellow) in Rat brain in cortex, hippocampus, cerebellum and nucleus accumbens of ventral striatum

Consequences of Pot Use

Acute (present during intoxication)
- Impaired short-term memory
- Impaired attention, judgment, and other cognitive functions
- Increased heart rate
- Anxiety, paranoia
- Psychosis (uncommon)
- Persistent (lasting longer than intoxication, but may not be permanent)
- Impaired learning and coordination
- Sleep problems
- Potential for marijuana addiction
- Impairments in learning and memory with potential loss of IQ
- Increased risk of chronic cough, bronchitis
- Increased risk of other drug and alcohol use disorders
- Increased risk of schizophrenia in people with genetic vulnerability**

Marijuana Effects

Health Risks
THC in your body has no real half-life. THC is a drug in a drug. It’s not only a substance, it’s a drug. Hence, it’s no surprise that marijuana has many health risks.

Cannabis Strains / Popular Types

Consequences of Pot Use

Acute (present during intoxication)
- Impaired short-term memory
- Impaired attention, judgment, and other cognitive functions
- Increased heart rate
- Anxiety, paranoia
- Psychosis (uncommon)
- Persistent (lasting longer than intoxication, but may not be permanent)
- Impaired learning and coordination
- Sleep problems
- Potential for marijuana addiction
- Impairments in learning and memory with potential loss of IQ
- Increased risk of chronic cough, bronchitis
- Increased risk of other drug and alcohol use disorders
- Increased risk of schizophrenia in people with genetic vulnerability**

Physiological Effects of Endocannabinoids

- Endocannabinoids are often produced as an adaptive response to cellular stress, aimed at reestablishing cell homeostasis
- Endocannabinoids affect a large number of physiologic processes including
  - Feeding behavior
  - Energy balance
  - Metabolism, and GI function
  - Pain perception
  - Motor control and posture
  - Learning, memory, and emotions
  - Immune and inflammatory responses
  - Cardiovascular function
  - Reproduction
  - Bone formation

*Courtesy of Dr. Gregory T. Carter 2012

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Main Phytocannabinoids
(480 chemicals in pot, ~66 are psychoactive)

Three most considered in medical pot:
• THC: Main psychoactive chemical, anti-emetic, appetite stimulant, anlagesia
• CBD (cannabidiol): much less psychoactive, anti-seizure, -spasmodic, -emetic, -inflammatory, analgesia, sedating, neuroprotective, Non-Reinforcing
• CBN (cannabinol): anti-seizure, -inflammatory, phase II sedative effects

Side Effects of Cannabinoids
– Disinhibition, relaxation, drowsiness
– Feeling of well being, exhiliration, euphoria
– Sensory - perceptual changes
– Recent Short-Term Memory impairment
– Balance/stability impaired
– Decreased muscle strength, small tremor
– Poor on complex motor tasks (e.g., driving)

Behavioral Effects of Concern
– Pseudohallucinations
– Synesthesias
– Impaired judgment, reaction time
– Pronounced motor impairment
– Increasingly disorganized thoughts, confusion, paranoia, agitation

Do Not Drive!
Impact of Alcohol & Substance Abuse on Adolescent Brain

Cannabis Use Disorder, Addiction

Darryl S. Inaba, PharmD., CATC-V, CADC III

Unmet Treatment Need Adolescent (% of AOD Dependence/Abuse without any private/public treatment)

9 in 10 Untreated

Prevalence
- 82.4 to 96.7%
- 82.2 to 92.3%
- 82.4 to 94.2%
- 84.3 to 90.0%
U.S.Avg.=92.2%

The Adolescent Challenge
Past Year Perceived Need for and Effort Made to Receive Treatment among Persons Aged 15-17 Needing But Not Receiving Specialty Treatment for Illicit Drug or Alcohol Use: 2007

Did Not Feel They Needed Treatment (1,776,000)
Felt They Needed Treatment and Did Not Make an Effort (40,000)
Felt They Needed Treatment and Did Make an Effort (15,000)

1.8 Million Adolescents Needing But Not Receiving Treatment for Illicit Drug or Alcohol Use

Source: NSDUH, 2007

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

Adolescent AOD Dependence/Abuse

Prevalence
- 6.0 to 9.2%
- 8.5 to 9.5%
- 9.1 to 9.9%
- 10.0 to 14.0%
U.S.Avg.=8.5%

Enigma of the Adolescent Brain (Age 12-25)

Erik Erikson: “most tumultuous of life’s several identity crises”

Shakespeare: “one should sleep out ages 10-23 because there is nothing but sorrow”

Freud: “An age of torturous psychosexual conflict”

G. Stanley Hall (in his 1904 seminal work: Adolescence): “A period of storm and stress”

Duke U. Study: 82.5% MH symptoms, 61.1% MH dx, 21.4% severe MH

Brain Development

• 20 weeks of gestation
  Sees proliferation and organization of neuron synapses

• 24 weeks of gestation to 4 weeks after birth witnesses rapid “pruning” of gray matter and increasing development of white matter throughout the brain

Age 12 – 25 Characterized by:

• Risky, Irrational, Unexplainable thoughts and behaviors
• Impulsivity, Novelty seeking
• Moody, Temperamental, Oppositional, Unpredictable changes in emotions and thoughts, raging libido (puberty)
• Illogical decision making and actions

Critical Periods for Brain Development (Windows)

• Windows of time in which brain must receive certain types of stimuli to develop optimally
• Axon myelination increases their “bandwidth” but inhibits new axon growth thus is crucial for adolescent learning but once it is done it is harder to change

Examples: vision, hearing, language (age 13), culture, social consciousness

The Human Brain: An Introduction

• At 4 weeks of gestation, brain cells – Neurons are forming at 250,000 per minute
• Brain is about 90% of its adult size by age 6
• Average adult brain has ~100 billion neurons and has formed 100 trillion synapses
• Neocortex is conscious human brain
• Mesocortex (Limbic System) is primitive survival, emotional brain

Genetic Propensity is not Inevitability

Brain of Psychopath can be overcome by Early Nurturing - Love

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.

Image via James Fallon
Two Main Waves of Gray Matter and Brain Development: Conception to 18 months then during adolescence

Generally development from rear the brain stem (basic functions-vision, movement, fundamental processing) slowly forward to prefrontal cortex (complicated thinking and decision making. Also
• Corpus Callosum thickens
• Hippocampus forms stronger links
• Frontal areas of goals and consequences matures

Adolescence: Individual acquires skills needed for self survival
Between ages 12 to 25
• Increased axon myelination results in up to 100 times increase in transmission ability
• Dendrites grow “twiggier”, 10 to 10,000 per neuron
• Synapses grow richer and stronger if used
• Unused synapses wither and are pruned
All this results in a faster, more sophisticated brain

Synaptic Density at birth, age 7 and age 15

Impact of Alcohol & Substance Abuse on Adolescent Brain

Steady ~1%/yr. pruning of grey matter and expansion of myelinated axons (white matter) from age 5

The brain works clumsily at first. But as it develops the adolescent brain is better able to integrate memories and experiences into better decision making by age 25 or so. As the developments occur the brain balances impulses, designs, goals, self-interests, rules, ethics and even altruism into decisions resulting in more sensible and complex behaviors.

Response Inhibition Research
Dr. Beatriz Luna, U of Penn

• 10 yo fail 45%, 15 yo succeed 70-80% almost the same as adults
• High Risk behavior increases dramatically at age 10-13, peaks at age 17 then drops precipitously to age 30 Steinbeige, Casey, Baird
• But, Teens take more risks not because they don’t understand the consequences but because the value the benefits more
Adaptive Adolescence

Risky behavior = more adaptive and novelty hungry, this primes them to move out of their safe and comfortable homes and into adulthood.

But this also makes them more vulnerable to drinking, drug use, erratic driving and crime consequences.

Also, Teens Trust and Listen More to Other Teens than to Adults

Cingulate Cortex with neurotransmitter Oxytocin activity develops before frontal cortex is fully developed. This makes social connections (bonding) more rewarding to adolescents. Teens therefore invest in future more than adults and seek out peer inclusion and acceptance during adolescence.  

Samuel Clemens, Richard & Mary Jessor

Synaptic Pruning

The first change after this synaptic growth spurt is a selective pruning which takes place.

In adolescence, most of this pruning is taking place in the frontal lobes. The adolescent loses approximately 3 percent of the gray matter in the frontal lobes.

Adolescent Brain Development: Myelination

• The second change is in myelination; in adolescence, it is not finished. The last part of the brain to myelinate is the frontal lobes. And myelination is not complete in the frontal lobes of the brain until around 18 to 20 or later.

• Myelination on a neuron allows it to operate more efficiently.

Gray vs. White Brain Matter

• Gray Matter: Neurons' cell bodies and dendrites Thinking portion of the brain

White Matter: Insulation (myelination) for neuron axons Enhances neuron communication ability, increases speed of synapses by 100 fold!
Late Frontal Cortex Development (Mid 20s and even up to age 40) correlates to future addiction:

A major reason why age of first use of alcohol or an addictive substance is best predictive indicator of future addiction problems.

Earlier the use - the greater probability of addiction

First Use at age 10 – 12 is 5X (500%) more prone to became addicted than first use at age 17 – 18 and 17 more prone than first use at age 25>

Andres, G. et al. (2004)
Last Area of Brain to Develop is Prefrontal Cortex

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

Addiction Is A Developmental Disease that starts in adolescence and childhood

Adolescent Pot User 2-4 X more likely to go on to other drug problems

Neocortex: Aware Human Brain

Mesocortex, Limbic System, Basal Ganglia: Unconscious Survival Brain

Adolescent Substance Abuse: America's #1 Public Health Problem

The Earlier Teens Use Any Substance, the Greater the Risk of Addiction

Why we all make such “great” decisions before age 25

Judgment last to develop

The area of the brain that controls “executive functions” — including weighing long-term consequences and controlling impulses — is among the last to fully mature. Brain development from childhood to adulthood.

Addiction Is A Developmental Disease that starts in adolescence and childhood

Adolescent Pot User 2-4 X more likely to go on to other drug problems

Neocortex: Aware Human Brain

Mesocortex, Limbic System, Basal Ganglia: Unconscious Survival Brain

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The Earlier Teens Use Any Substance, the Greater the Risk of Addiction

Reasoning, Impulse Control, Temporal Processing, Planning, Judgment.

Who made great decisions before age 25

Premotor 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

Why we all make such “great” decisions before age 25

Don’t make such decisions before age 25.
Prefrontal Cortex of the Neocortex

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

*Note: Takes until mid 20s to become functional and to 40s to fully “hard wire”*

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!

Electron Microscopy of Neurons, Dendrites and Axons

Early (<18y) Long-Term Cannabis Use Decreases Axonal Fiber Connectivity

By Age 6 100 Billion Neurons and Development of a Quadrillion Synapses

Marijuana – Schizophrenia ↓IQ Controversy

- Smith, MJ, et al. (2013) also cognition and memory problems (37 X less than non-users
- DiForti, M, et al. (2013) – 6 year earlier onset of psychosis if daily use started age 15 or <
Persistent Marijuana Users Show A Significant IQ Drop between Childhood and Midlife

Followed 1,037 individuals from birth to age 38. Tested marijuana use at 18, 21, 26, 32 and 38. Tested for IQ at ages 13 and 38.

Average Point Difference in IQ score (IQ at age 13 – IQ at age 38)

Non-users | used 1 Dx | used 2 Dx | used 3 Dx

Source: Meier MH et al., PNAS Early Edition 2012

Smaller brain regions associated with long-term heavy marijuana use

L (yellow) and R (blue) amygdala and (red) and R (green) hippocampus

Shape and function of hippocampus has been linked to reduced memory performance in heavy cannabis users.

Yucel et al., Arch Gen Psychiatry. 2008 Jun;65(6):694-701.

Cannabis-Related Memory deficits and hippocampal differences

Hippocampal and amygdalar volumes were smaller in cannabis users than in controls.

Shape and function of hippocampus has been linked to reduced memory performance in heavy cannabis users.

Smith, MJ et al. 2015

Long-term effects of marijuana use on the brain

Filbey, FM et al. (2014) PNAS 111(47):16913-16918 UC Davis

Significant reduction in gray matter volume of bilateral orbitofrontal gyri of Marijuana uses compared with controls.

Source: Courtesy of Daniel Amen, M.D.
Also, Structural/functional connectivity of OFC regions and OFC with Temporal Gyri increased in pot users

Too much or too little connectivity isn’t Good for brain function. An equal Balance is needed

Filbey, FM et al. 2014, PNAS

Regular Cannabis Use Increases Schizophrenia Risk in those with AKT1 rs244732 genotype

AKT1 genotype does not predict History of Cannabis use (p=0.772)  GXE multiplicative model: p*=0.014

Di Forti et al., Biological Psychiatry, 2012.

Adolescent THC Exposure Decreases Dendritic Branching During Development of PFC Pyramidal Neurons

Adolescent THC exposure = premature pruning of Dendritic Spines of PLC Pyramidal Neurons

Adolescents who Smoke Cannabis have Increased Risk of Schizophreniform Disorder, Depending on the COMT Gene

“Skunk” (16% THC) Marijuana and Risk of Psychosis

• 2015 British Study: English “Skunk” pot is high potency pot ~ 16% THC, low CBD
• Occasional or weekend use increased psychosis risk 3X more than non users
• Daily use increased risk is 5X more than non users
• N = 410 first episode psychosis, 370 controls

Enlarged Ventricles involved with loss of Grey Matter in Schizophrenia

Marijuana and Anxiety Disorder
14 yr olds using occasionally, weekly, or daily over 15 yrs are 2.5 x as likely to have anxiety disorder at age 29
If non-using at age 29, they are still 2 x as likely to have anxiety disorder
RD Schwartz-Bloom, Duke Univ. Medical Center 2012

Depression and Suicidality
Linskey, MT. et al. (2004), Arch. Gen. Psych. 61(10):1026
Discordant Twin with early marijuana use (<17) was 3.5 times more likely to attempt suicide than their non early use twin

Cannabis-Associated Psychosis

CANNABIS AND SCHIZOPHRENIA
Study of Swedish Conscripts (n=45,570)

Cases of schizophrenia per 1,000
0 5 10 15 20
No of times cannabis taken


CANNABIS AND SCHIZOPHRENIA-Like Longitudinal prospective Dunedin study (n=437)

Risk of schizophrenia-like psychosis at age 26 years

4.5
1.6
Cannabis users by age 15 years
Cannabis users by age 18 years
Arseneault et al BMJ 2003

Earlier Use of Marijuana is Associated with Lower mo-Prefrontal Cortex Volume

JC Churchwell et al. 2010

More Use of Cannabis Associated with Worse Social Outcomes at Age 25 (New Zealand Study)

% welfare dependent (ages 21-25)
% Unemployed (ages 21-25)
mean personal income in thousands of NZ $ at age 25
% gained university degree by age 25

# of occasions using Cannabis ages 14-21


Medical Marijuana States Have Higher Youth Marijuana Use Rates

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

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AKT1 Gene Variations and Psychosis

Never used cannabis
Used cannabis at week ends or less
Used cannabis every day
Persistent Marijuana Users Show A Significant IQ Drop between Childhood and Midlife

Followed 1,037 individuals from birth to age 38. Tested marijuana use at 18, 21, 26, 32, and 38. Tested for IQ at ages 13 and 38.

Average Point Difference in IQ score

<table>
<thead>
<tr>
<th>IQ at age 13 - IQ at age 38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-users</td>
</tr>
<tr>
<td>used</td>
</tr>
<tr>
<td>used</td>
</tr>
<tr>
<td>used</td>
</tr>
</tbody>
</table>

Source: Meier MH et al., PNAS Early Edition 2012

Greater IQ loss with cannabis use disorder severity and age of disorder

Pot IQ Study ruled out: use within the past day or week, tobacco depn., hard drug depn., alcohol depn., & schizophrenia on IQ loss

Source: Meier et al. 2012

Courtesy of Daniel Amen, M.D.
Persistence of IQ drop from adolescent and even adult pot use measured at age 38

Meier et al. 2012

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Filbey, FM et al. (2014) PNAS 111(47):16913-16918 UC Davis

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Filbey, FM et al. 2014, PNAS

Cannabis-Related Memory deficits and hippocampal differences
IQ Drop Persists in Adults who use Marijuana Infrequently if they Smoked Weekly Before Age 18

MH Meier et al. 2012

Cannabis-Associated Psychosis

CANNABIS AND SCHIZOPHRENIA
Study of Swedish Conscripts (n=45576)

Cases of schizophrenia per 4,000

No of times cannabis taken


CANNABIS AND SCHIZOPHRENIA-Like
Longitudinal prospective Dunedin study

Risk of schizophrenia-like psychosis at age 26 years

Cannabis users by age 15 years

Arseneault et al BMJ 2002

Cannabis users by age 18 years

Schizophrenia from drug induced psychosis more likely drug precipitated in vulnerable users

• Swedish National 84 mo. Follow up N=7,606
• Those with ↑ genetic risk for SUD and Mod. Risks for psychosis progressed onto Schizophrenia at highest rate 11.3%
• These were lowest for alcohol and highest for cannabis experienced psychosis


Also 11 site Europe and Brazil study confirms psychotic disorders association with cannabis use predictable most by daily or high potency cannabis use.


Regular Cannabis Use Increases Schizophrenia Risk in those with AKT1 rs2494732 genotype


Adolescents who Smoke Cannabis have Increased Risk of Schizophreniform Disorder, Depending on the COMT Gene

Caspi et al., 2005

Enlarged Ventricles involved with loss of Grey Matter in Schizophrenia

High Potency Cannabis and Earlier Onset of Psychosis

Odds Ratio

<table>
<thead>
<tr>
<th>AKT1(T/T)</th>
<th>AKT1(C/T)</th>
<th>AKT1(C/C)</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≤ Weekly</td>
<td>31.4</td>
<td>31.1</td>
</tr>
<tr>
<td>Weekly</td>
<td></td>
<td>29.4</td>
</tr>
<tr>
<td>Daily</td>
<td></td>
<td>26.5</td>
</tr>
</tbody>
</table>
| High Potency Cannabis and Earlier Onset of Psychosis

Risk of schizophrenia by age of cannabis exposed

Di Forti et al., Biological Psychiatry, 2002.
“Skunk” (16% THC) Marijuana and Risk of Psychosis

- 2015 British Study: English “Skunk” pot is high potency pot ~ 16% THC, low CBD
- Occasional or weekend use increased psychosis risk 3X more than non users
- Daily use increased risk is 5X more than non users
- N = 410 first episode psychosis, 370 controls


Marijuana &/or Alcohol use predict school, health, mental health problems

- Higher Alcohol Use = ↑ unpreparedness and delinquency in high school
- Higher Pot Use = ↑ unpreparedness, delinquency and ↓ academic performance and mental health in high school
- Asian, black, Hispanic youth had worse results plus poorer physical health in high school


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Depression and Suicidality


Discordant Twin with early marijuana use (<17) was 3.5 times more likely to attempt suicide than their non early use twin

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


Study Shortcomings:
* Increase in adolescent Pot and illicit drug use began in 2009, study was from period before recreational use legalized in Co., etc.
* Study was of NSDUH and MTF reports on Adolescents from all states. More recent reports are contrary especially in States that legalized recreational pot use

Grueza, RA et al. (2016) JAACAP 55(6)


* intoxication with memory and motor impairments. More potent forms leads to risks like anxiety, agitation, paranoia and psychosis
* Used during pregnancy than any other drug and is associated with lower birth weights
* Frequent use by youths associated with risk for opioid abuse, alcohol abuse, and major depressive episodes
Marijuana Addiction
Cannabis Use Disorder

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

- Alcohol: 94.5%
- Prescription Opioids: 3.9%
- Marijuana: 18.7%
- Cocaine: 4.3%
- Tranquilizers: 2.3%
- Heroin: 1.7%
- Hallucinogens: 1.2%
- Stimulants: 1.0%
- Sedatives: 0.8%

NSDUH 2012

MARIJUANA ADDICTION

- 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-SSATS 2012

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

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.

NESARC: National Epidemiologic Survey on Alcohol and Related Conditions

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

Addiction: About 9% of Pot users may become dependent, 1 in 6 who start in adolescence and 25-50% of daily users.

Estimated Prevalence of Dependence Among Users

American Psychiatric Association's Diagnostic Manual (DSM) has included marijuana use disorders since 1980. 2013 DSM-5 added Marijuana Withdrawal as a diagnosis & Pathologic Gambling Disorder: 0.4-1% of all who gamble est. to meet Diagnostic Criteria.

CHRNA2 Gene implicated in those who develop Cannabis Use Disorder

- GWA Study of >50,000 (2,387 with CUD and 48,985 controls)
- Cannabis ↑ risk for schizophrenia and schizophrenia ↑ risk for CUD
- Also some link to ↓ Educational performance and attainment but not always so


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: ↑ 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

Cannabis-Related Disorders
Tolerance, Dependence, Withdrawal

- Cannabis Use Disorder
- Cannabis Intoxication
- Cannabis Withdrawal
- Other Cannabis-induced Disorders
- Unspecified Cannabis-Related Disorders

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

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.

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

Break Time
**Brief Review of Addiction Treatment**

**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

**TREATMENT CONTINUUM**
- Detoxification
- Initial Abstinence
- Long-term Abstinence
- Recovery

**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 (craving)
- bupropion,
- buspirone
- divalproex,
- naltrexone,
- lithium, antidepressants,
- Gabapentin (withdrawal and craving) and
- Replacement Tx: Nabiximols® (Spray with 25.7mg THC and 23.8mg CBD)
Developing Medications: N-Acetylcysteine for Marijuana-Dependent Adolescents

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

Cognitive Impairment
11.3% of Limbic system of which 7.8% of Hippocampus plus 24% of dopamine transporters
- Attention, memory, understanding problems
- Word meaning, problem solving, Stroop paradigm
- Inflexibility, abstract thinking, judgment
- Temporal processing: planning, processing goals, delayed discounting

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

Endogenous or Intrapersonal Craving Triggers
- Any Negative Mood State
- Boredom
- Fears
- Anxiety or depression
- Anger/resentments
- Guilt and Shame
- Others:
  * dishonesty, exhaustion, cocky, complacent, self-pity, overconfidence, impatience

Normal Brain
Marijuana Abuse

Courtesy of Daniel Amen, M.D.
Any Negative Mood State can initiate a Craving Reaction

• HALT – Hungry, Angry, Lonely, Tired
• RIID – Restless, Irritable, Isolated, Discontent
• BAAD – Bored, Anxious, Angry, Depressed

Craving can be caused by the sight, smell, and taste of

* a using partner
* a using place
* a dealer
* cash
* the drug itself

Environmental or Interpersonal Triggers and Cues via Dendritic Emotional Memory “Spines, Bumps, or Protrusions”

Environmental or Interpersonal Triggers and Cues

• Any Sensory Input to addiction memories: visual, odor, auditory, physical withdraw, etc. – PTSD?
• Thoughts of using or of withdrawal
• Other Interpersonal factors: relationship problems, social/vocational pressures, no support system, negative life events, untreated dual diagnoses

Amygdala not lit up
Nature Video

Amygdala activated
Cocaine Video

Courtesy of Anna Rose Childress, Ph.D.
Craving Extinction & The Resilient Brain


Physiology of Craving

- Increased heart and pulse rate
- Specific electrical changes in skin activity and spindle effects on EEG
- Increased peristalsis activity of gut
- Pupil dilatation and cortisone stress reaction
- Two degree or more core temperature drop

Childress, AR, McLellan T, O'Brien CP Br. J. of Addict. 1986
Craving “Tool Kit”: Effective Relapse Prevention Techniques
- Networking, Sponsor, Journaling, 12-Steps
- Emotional Freedom Techniques (EMDR, Brain Spotting, Tapping, Elastic Snapping)
- Yoga Breaths, Somatics, Figure 8 Pacing
- Prayer, Mindfulness Meditation, Grounding Interventions, Acupuncture, Laughter Yoga
- Consequence Reminders (family photo, car keys, consequence cards)
- Paradoxical Interventions (emptied Librium capsules, empty Copenhagen can, turn shirt inside out, wash off and reapply makeup, et al.)

Post Acute Withdrawal Syndrome (PAWS)
- Sleep Disturbances – insomnia, nightmares
- Memory Problems – Short-term, learning
- Thought Problems – concentration, rigidity, repetitive, abstract thinking & problem solving difficulties
- Anxiety & hypersensitivity to stress
- Inappropriate emotional reactions, mood swings
- Physical and coordination difficulties
- Syndrome persists for 3-6 months, sleep problems maybe longer

PAWS Treatment
- Clinical: CBT “grounding exercises”
- acamprosate for alcohol PAWS
- carbamazepine (Tegretol)
- Trazodone
- naltrexone

5. Mental Health and/or other Co Morbid Medical Conditions Must be Stabilized and Medically Managed During Recovery
May be Pre-Existing or Addiction-Induced?

Mental Health and/or other Medical Conditions Must be Stabilized and Medically Managed During Recovery
May be Pre-Existing or Addiction-Induced?

Major Axis I Disorders
- Thought Disorders (Schizophrenia) 0.7-1.4% ap
- Affective Disorders (Depression) 8.6% ap, 15% lp
- Mood Disorders (Bipolar) 1.2% ap
- Anxiety Disorders & Phobias 16.4% lp
- Substance Use Disorders soon to be Addictions and Related Disorders 9-12% ap, 30% lp
- Adjustment Disorders relatively high depending on cause
- Pervasive Developmental Disorders Mental Retardation 0.78%, Developmental Disabilities 1.49%
**Four Quadrant Model: A Treatment Guide?**

<table>
<thead>
<tr>
<th>Quadrant 4</th>
<th>Quadrant 3</th>
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<tbody>
<tr>
<td>More Severe Mental Disorder with More Severe Substance Use Disorder</td>
<td>Less Severe Mental Disorder with More Severe Substance Use Disorder</td>
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<tr>
<th>Quadrant 1</th>
<th>Quadrant 2</th>
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<tr>
<td>Less Severe Mental Disorder with Less Severe Substance Use Disorder</td>
<td>More Severe Mental Disorder with Less Severe Substance Use Disorder</td>
</tr>
</tbody>
</table>

**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

**RECOVERY**

**The Resilient Brain**

8-10 Months Rigorous Uninterrupted Treatment for Best Outcomes
Implies time needed for brain to become functional
Takes up to 2 years for greater functioning to return

**Research on the Brain in 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

Courtesy of Nora Volkow (Volkow, Hitzmann, Wong, et al 1992)
52

Dopamine Transporter Binding (DAT) Recovery in Meth Addiction

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

Science of Addiction & Recovery: Dispelling The Stigma

Darryl S. Inaba, PharmD., CATC-V, CADC III
Director of Research & Education – CNS
Director Clinical & Behavioral Health Services - ARC

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)
- Irresponsible pleasure seekers: Willful Misconduct?
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

CNS Addiction Pathway

Survival/Reinforcement Circuit

Control Circuit

Go Switch

Stop Switch

Brains Addiction Pathway

Location of the nucleus accumbens in human CNS

Blum K. et al. (2014)

Brain on Cocaine

Minutes after shooting or smoking

Cocaine affects addict’s brain differently than a Normies brain
VTA Dopamine Cells of Opiate Addict vs. Non Addict Rat

Control Circuitry = Stop Switch
- Orbital Prefrontal Cortex – Especially left ventral medial OFC
- Fasciculus Retroflexus (anterior)
- Lateral Habenula (posterior and mesocortex terminal)

Medial Prefrontal Cortex: Value
Lateral Prefrontal Cortex: Consequence

Diffusion Tensor Imaging
Go – Stop Disconnect also viewable by PET Scans

Addiction is a battle between the old primal brain and the new brain

Relapse Related Brain Circuits and Processes
- Stay Stopped (Slip Decisions)
- Emotional Memory (Cravings)
- Stress Hormone Cycle (Hypersensitivity)
Slip/Stay Stopped Brain Anomalies

Brain Processes of Relapse

A. Slip/Stay Stopped Brain Anomalies

B. Memories

Formation & Role In Drug Cravings

Neuro-development of Memories

Dendritic spines, bumps or protrusions
**Dendritic Memory Spines**

- Amygdala process emotional memories, hippocampus all other memories
- Also known as Bumps, Spikes – I like the term memory protrusions = less triggering
- 4 to 6 sensory inputs of the same stimulus per hour results in development of a semi-permanent memory protrusion
- The more often a memory protrusion is activated the larger it grows and the more permanent it becomes

---

**Meso-Limbic Reward-Reinforcement Circuitry of the MFB**

- **Phase I** – Endogenous/Environmental Cue or memory triggers the Ventral Tegmental Area to release dopamine which activates core of Nucleus Accumbens Septi = anticipation of use **ON A MISSION! If initiated difficult to stop**
- **Phase II** – Cues or actual use of addictive drug activates dopamine “go” switches of lateral hypothalamus and Nucleus Accumbens (core and shell): **COMPULSION FOR MORE!**
- **Phase III** – Control circuitry of the prefrontal cortex is disrupted, is inactivated and releasing glutamate: **results in LOSS OF CONTROL, CONTINUE DESPITE NEGATIVE CONSEQUENCES**

---

**New NIH Details on Addiction Craving Brain Pathway**

- Hippocampal memory process activates
- Lateral Septum via glutamate and this in turn activates
- Ventral Tegmental Area (VTA) via gamma-aminobutyric acid (GABA) that then activates
- Nucleus Accumbens Septi (“go Switch”) via dopamine

Brain Processes of Relapse

C. Stress Hormone Cycle Hypersensitivity

Addictive drugs first release of dopamine in the midbrain fools it as being a coping mechanism for the relieve of stress

- Opiates & endorphins shown to also inhibit CRF & ACTH as cortisol would naturally do
- But, withdrawal from opiates cause increase release of CRF, ACTH and creates hypersensitivity to stress that overrule cortisol’s regulation of cycle = craving
- Cocaine directly releases the CRF and ACTH mistaken as part of or covered by the rush, stimulant withdrawal also activates the stress mechanism = craving
- Research: metyrapone validation (shuts off cortisol production increasing CRF & ACTH) and CP-154,526 treatment (blocks CRF and thus suppresses ACTH release)

Heilig and Koob 2007, Lowey et al. 2008

Hypersensitivity of Stress Hormone Cycle in Addiction

VTA’s (ventral tegmental area): GABA-releasing neurons, dopamine-releasing neurons and Kappa opioid receptors interaction in stress. Drugs and natural satiations release dopamine in the VTA. GABA applies a brake to this via strengthening synapses (known as long-term potentiation or LTP) but stress interrupts this process leading to unabated dopamine reinforcement. Nor-BNI blocks Kappa receptors in the VTA and prevents stressed out rats from relapsing to cocaine use

Graziane, Poitier, Brand, Pierce, Kauer (2013), J. Neuron

Addiction is a stress-induced defect in midbrain’s ability to perceive pleasure

- CRF & ACTH are neurotransmitters as well as hormones they modulate novelty-seeking and dopamine activity in the brain
- Severe stress increase risk-taking behaviors in all and suppress dopamine’s ability to perceive reward, survival reinforcement, “pleasure?” resulting in anhedonia since
- CRF & ACTH as neurotransmitters produce the unpleasant emotional reactions associated with stress
- Cortisol usually turns off these secretions to terminate a stress reaction but extreme stress overrules cortisol

“Addiction is a battle between the old primal brain and the new brain

Fish        Cat       Chimpanzee        Human fr. SMA
Old Brain = Survival (5X faster and more powerful) than Neocortex = Control, Planning and Decision Making

© 2007, CNS Productions, Inc.
Historic Evolution of Addiction Science

Dr. James Olds, McGill University
Toronto, Canada 1954
Operant Conditioning

Dr. Terry Robinson
U of Michigan 2004
Incentive Sensitization Research Confirmation
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
15.3% of Rats Preferred Alcohol over sweet water and increased pursuit of it despite having to suffer foot shocks or bitter quinine added to the drink.

Leffler K [U of Gothenburg]; Blum et al. [U of Texas] 2018

89 genes associated & > 900 suspected
- CREB
- CHRM2
- CNR1
- GABRA2
- Leu-Pro allele
- NQD2
- ADH4
- KMALDH1
- COMTmet158met
- DRD3 Allele
- Tipsy Gene: CYP2E1
- AUTS2

2010 NIDA Genome Wide Association Study (GWAS)

CHRNA2 Gene implicated in those who develop Cannabis Use Disorder
- GWA Study of >50,000 (2,387 with CUD and 48,985 controls
- Cannabis ↑ risk for schizophrenia and schizophrenia ↑ risk for CUD
- Also some link to ↓ Educational performance and attainment but not always so


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

Trauma & Adverse Childhood Experiences (ACE)
Experience of Violence & Victimization (sexual/physical abuse, severe neglect, loss, domestic violence and/or witnessing of violence, terrorism or disasters)
National Association of State Mental Health Program Directors 2006

Childhood trauma shapes a child’s beliefs about their identity, world view and spirituality
Epigenetic Expression

Epigenetic Expression

Epigenetic Expression

Epigenetic Expression

Identical Twin Mice with Divergent Epigenetic Expression

Even Identical Twin with Epigenetic Expression of Different Races

Chang and Eng Bunker Conjoined Identical Twins born 1811

MAOA Gene Expression, Childhood Trauma and Antisocial Behavior

Methylation, Acetylation, Phosphorylation of genetic peptide and 5hmC tags result in altered expression of genes
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

Neuron Homeostasis: Brain in Dynamic Equilibrium

THC in Marijuana Mimics Brain's Anandamide

Drugs Mimic, Disrupt, or Block Neurotransmitters

SOME EXAMPLES -
UPPERS: Catecholamines (Norepinephrine, Epinephrine, Dopamine) + Serotonin and Acetylcholine
DOWNERS: Endorphin, Enkephalin, GABA, Serotonin
PSYCHEDELICS: Serotonin, Acetylcholine, Alpha Psychosin, Norepinephrine, Dopamine, Anandamide & endocannabinoids

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.

Also Excess Nor Epinephrine (Nor Adrenaline) and Less Transporters in Pathological Gamblers

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.

2012 UCSF Research Confirms Role of Endogenous Opioid Neurotransmitters in Reward Circuitry as well as Dopamine

Serotonin aka 5-hydroxytryptamine also involved with all addictions?
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

Van Loere et al., 2007
Hirvonen et al., Mol Psychiatry 2012

Cannabinoid CB1 Receptors in Human Brain are Lower in Marijuana Abusers

Van Laere, K et al. 2009

High Novelty Seekers have Low CB1 Receptors (CBR)
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 extavagance needy have low CB₁ receptors.

K Van Laer et al., 2009

Addiction Pathology via new neuroimaging techniques

Anatomical (Structure)

CT/CAT, MRI/MRI-GUI, X-Ray,
dMRI, DTI

Functional

ASL, DOI/DOT, EEG, EROS,
fMRI/ Bold fMRI, MEG, PET,
SPECT, SPM, et al. Scans

Levels of Use
- Abstention
- Experimental
- Social / Recreational
- Habitual
- Abuse
- Addiction

Multiple Brain Imaging Techniques

15 year old male non-drinker
15 year old male heavy drinker
<table>
<thead>
<tr>
<th>Cocaine Abuse</th>
<th>Alcoholism</th>
<th>Obesity</th>
<th>Tobacco</th>
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<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
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(Courtesy of Wang, Volkow, Panayotis & Fowler (2004))

Normal Brain  
Marijuana Abuse  
(Courtesy of Daniel Amen, M.D.)

Normal Brain  
Methamphetamine Abuse  
(Courtesy of Daniel Amen, M.D.)

Video Presentation (37 Minutes)  
CNS Productions, Inc.

Marijuana: Neurochemistry & Physiology

Questions/Comments?

Chronic Alcohol Abuse  
Heroin Abuse  
(Courtesy of Daniel Amen, M.D.)

Medical Marijuana:  
Potential Treasure Trove of medically useful molecules or a Pandora’s Box of Harmful/Addictive Molecules

Also Colorado Experience, Health Impact (Lungs, Heart, MH and Pregnancy), Industrial & Medical Marijuana, Drug Interactions, and Urine Drug Testing Issues
Over 100 different Cannabinoids with different effects identified so far in marijuana.

CANNABIDEROL

Cannabigerol (CBG)
The Mother Cannabinoid

TETRAHYDROCANNABINOL

THC

Cannabinol

CANNABIDIOL

HISTORY

- 8,000-4,000 BCE use by early man
- 2727 BCE Earliest recorded human use
- 100-0 BCE Psychotropic effects noted
- 70 Nero’s army list it as a medicine
- 1378 Ottoman edict against hashish
- 1611 King James mandates production of hemp in Virginia
- 1906 PF & Drug Act: Pot is a poison
- 1914 Harrison Act: use is illegal
- 1937 Marijuana Tax Act
- 1970 NORML is founded
- 1996 CA first medical marijuana law
- 2014 CO first legal recreational use
Shen Nung 2737 BC
Tested 365 herbs

Cannabis traces (still active) found in 3,000 y.o. Egyptian mummies

Dr. W.B. O’Shaughnessy introduced marijuana into Western medicine during the 1840’s

Medical Marijuana pre-1937 prohibition
Cannabis Tincture Parke Davis 1910
1906 Cannabis for Neuropathic Pain

Cannabis for Neuralgia 1925

Marijuana Prohibition 1937-38
Pancho Villa
William Randolph Hearst
Harry J. Anslinger
Rocky Mountain High Intensity Drug Trafficking 2015 Vol. 3 Impact Report notes that between 2013 and 2014:

- Marijuana related traffic death ↑ 32% and positive THC DUI ↑ 45%
- Marijuana-only poison control reports ↑ 72%, pot related ER visits ↑ 29%, hospitalizations ↑ 38%
- Use by children age 12 to 17 59% higher than national average and
- 34% increase illicit marijuana trafficking

Colorado Data

In 2015 Colorado 12-17 yo Pot use 56% > national average

PAST MONTH MJ USE AMONG CO TEENS - YRBS

PAST MONTH MJ USE – COLORADO, DENVER, BOULDER – YRBS
Past month prevalence of marijuana use - 12+ yrs

Source: National Survey on Drug Use and Health

ADAMS COUNTY YOUTH INITIATIVE 2013
IF YOU WANTED TO GET ALCOHOL/MJ, HOW EASY WOULD IT BE TO GET?

Maryjuana Alcohol

Easy/Sort of Easy Hard/Sort of hard Easy/Sort of Easy Hard/Sort of hard

27.0% 63.0% 27.7% 62.3%

Number substance treatment admissions for marijuana - Denver metro

Source: Drug/Alcohol Coordinated Data System

MONITORING THE FUTURE, 2012
IF YOU WANTED TO GET ALCOHOL/MJ, HOW EASY WOULD IT BE TO GET? - 8TH GRADERS

Blood tests for DUID positive for THC - Colorado

THC + DUID increased 45% in 2014 from 2013

Source: RMHIDT Impact Vol 3 2015 & Colorado Department of Public Health and the Environment
Use of regulated marijuana by Denver teens

Source: Salomonse-Sautel et al. (2012), JAACAP 51:654-702; Thurstone et al., under review

Average urine drug screen results

Source: Thurstone et al., in preparation

Drug-Related Suspensions/Expulsions - Colorado

Source: Colorado Department of Education

TRAFFIC FATALITIES WITH A THC+ DRIVER

Marijuana related Colorado traffic deaths ↑ 32% in the 2014 vs. 2013

Washington State: Marijuana now most frequently found drug in fatal crashes 2014


ED visits by substance - Denver Metro 2010

Source: Drug Abuse Warning Network

Marijuana - 20%, n= 2031
Hospital Discharge Diagnoses - Denver Metro

Colorado State pot-related hospitalizations ↑ 38% in 2014 from 2013

Sources: RMHIDT Impact Vol. 3 2015 & CDPHE, Colorado Hosp Assoc Discharge Data Program

Co. Pot Tourists More Likely Than Locals to go to ER 2016

Healthy Mucous Membrane

Marijuana Abuse Impact on Health

Smoking Pot: Impact on Respiratory System

Mucous Membrane of Marijuana Smoker

Mucous membrane's of marijuana smoker who also smokes cigarettes
Marijuana (cannabinoids) suppression of Immune System, Lung Cancer Controversy: CBD vs. other cannabinoids?

THC and other cannabinoids trigger massive mobilization of myeloid derived suppressor cells (MDSCs) to suppress the human immune system to infections and cancer.

Negative Impacts of Marijuana on Health

- 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
- ↓ IQ by 8 points & ↓gpa and implies pot quickened or induced schizophrenia. Healthy subjects scored 37 times higher on memory tests! Effects persist years after abstinence
- ↑ Heart rate 20%-100% and persists for 3 hrs and ↑ risk of heart attack 4.8 fold in first hour of use
- Addiction, sleep problems and concern of second and even third hand marijuana exposure

Marijuana and the Testicles

CB Receptors in testis

Marijuana Significantly Increases Risk of Testicular Cancer (non-seminous)

- Dahling 2009 Ages 18-44 100% current users: 2 x as likely overall, 3 x as likely if 1st use < age 18, 3 x as likely if used weekly
- Trebert 2011 Ages 18-50 < 10% current users: 2 x as likely overall, 3 x as likely if used daily, 75% had 1st use < age 18
- Lacson 2012 Ages 18-35 33% current users: 2.5 x as likely if ever used, 3 x as likely if a former user, 3 x as likely if < 1/week, 3 x as likely if < 10 years, 6.5 x as likely if > 10 years

Occlusion of Brain Arteries but Recovery with Cessation of use

Use started Age 20

MARIJUANA (THC) & Pregnancy

NSDUH 2009 results

- 7.6-9% of U.S. used marijuana in past 30d
- 3-16% of pregnant women used in past 30d
- Compared to nicotine and alcohol pot use is least likely to be reduced during pregnancy
- THC half-life is 25-57 hours and can be detected in body for 1 to several months
Treatment Admissions for marijuana use during pregnancy

Effects on Pregnancy Continued

Marijuana use during pregnancy also associated with:

- 1.5 times greater risk of having an autistic child  
  Corsi, DJ et al. (2020) Nat. Med.
- 2.3 times greater risk of stillbirth  
  NIH (2013) Network Study

THC UA Prevalence in Pregnant Women

One anonymous study of urine samples from 322 consecutive pregnant women admitted to an Illinois hospital found a 19.9% were positive for marijuana


Marijuana Effects on Pregnancy

• “Fetal Marijuana Syndrome”? smaller head size with memory, learning, behavioral & verbal reasoning problems

• Impact on moms: premature labor, prolonged or arrested deliveries, increased bleeding, increased Cesarean deliveries, meconium staining, increased manual removal of placenta, maternal anemia

Marijuana Effects on Pregnancy

Controversy: controlled human studies impossible and most use alcohol or other drugs along with pot

- Lower birth weight and gestational period
- Neurondevelopment and endocannabinoid development problems
- Neonate abnormal response to light or visual stimulus, “startles”, tremulousness, drug withdrawal high pitch cry
- Attention, concentration, judgment, memory, and problem-solving difficulties; ADHD/ADD; psychosis, delinquency and link with Stillbirths & SID

Rat Models demonstrate low dose regular use significantly impact placental and fetal development

This resulted in:

8% decrease in birth weights and
>20% decrease in both brain and liver growth

THC in Breast Milk

- Moderate levels (0.8% of mom’s dose/kg detected in her breast milk)
- Higher levels in breast milk than in maternal serum with chronic heavy use
- No validated reports on infant impact but may contribute to sedation, weakness and poor feeding of marijuana exposed babies
- Potential to lower oxytocin and thus decrease release (let down) of milk during feeding

Hemp = variety of non-psychoactive C. sativa
(≤ 0.3% THC)

- Fibers for rope, canvass, cloth, twine and paper- U.S. Constitution printed on Hemp paper 1790, composite board, drywall, insulation
- Oil for fuel, lubricants, cosmetics, varnishes, plastics
- Seeds for bird food, proteins and essential oils for humans

Industrial Marijuana Hemp

Hemp cultivated non-food plants:
fiber for rope, clothes, paper and seeds for oil and birdseed

33 States and D.C with Medical Pot Laws
2018 & 11 (Co., Wa., Or., Al., Ca., Nev., Maine, Vt., Mich., Il., ) + DC permit Recreational Use as of 2019

2012 Meta Analysis of National Surveys:
Residents of Med. Pot States have:
- Higher rates of Pot Use
- Higher rates of Pot abuse/dependence
- Much Lower Adolescent Perception of Pot being Harmful and
- Much Higher Adolescent Average Pot Use As compare to States with no Med. Pot Laws

Medical Marijuana pre-1936 prohibition

Cannabis Tincture Parke Davis 1910

1906 Cannabis for Neuropathic Pain

Cannabis for Neuralgia 1925

Historic & Current Medical Uses
- Treat Insomnia
- Calm anxiety
- Treat venereal disease
- Calm coughs
- Control spasms
- Relieve childbirth pain
- Calm migraine headaches
- Relieve glaucoma
- Control pain & nausea
- Induce weight gain

Not a Single Major American Health Association Accepts Smoking Crude Marijuana as Medicine

National Cancer Institute
American Cancer Society
National Eye Institute
National Glaucoma Society
American Academy of Ophthalmology
National Multiple Sclerosis Society
American Medical Association

Need to Note Conditions Specified:
- Short-Term use only (< 6 months)
- Documented failure of all other medications
- Only under ongoing medical supervision
- MD routine monitoring for positive outcomes
- MD Review Board to provide guidance for use in specific patients
- Smoking is crude and hazardous delivery system so endorse use of different chemicals

Institute of Medicine Medical Marijuana (chemicals) Endorsement 1982
Vice Adm. Jerome Adams, Surgeon General Releases Advisory on Marijuana’s Damaging Effects on the Developing Brain 8/29/19

- Intoxication with memory and motor impairments. More potent forms lead to risks like anxiety, agitation, paranoia and psychosis.
- Used during pregnancy than any other drug and is associated with lower birth weights.
- Frequent use by youths associated with risk for opioid abuse, alcohol abuse, and major depressive episodes.


- Alzheimer’s, ALS, cachexia/wasting syndrome, cancer, chron’s epilepsy & seizures, glaucoma, HCV, HIV, MS & muscle spasticity, severe & chronic pain, nausea, PTSD.
- Insufficient evidence to support medical marijuana for most of these conditions.
- Moderate support for effective use in cachexia/wasting and some support of use in pain but need dosing and side effect profile.

Projected Symptoms that can benefit from Medical Marijuana  Collins, S (2014), Phcy Today 20(4)

- Aggression1
- Anxiety1
- Arthritis2
- Asthma2
- Back pain2
- Chronic pain1
- Cystic fibrosis2
- Depression1,2
- Drug withdrawal1
- Epilepsy2
- Excessive saliva1
- Glaucoma/ocular pressure1,2
- Gonorrhea1
- Herpes2
- HIV-related pain1
- Inflammation1
- Insomnia2
- Loss of appetite/weight loss1,2
- Mania/psychosis1,2
- Multiple sclerosis2
- Muscle spasms1,2
- Nausea1,2
- Rheumatism2
- Skin conditions1
- Stress2
- Tobacco-associated phlegm1,2
- Tumor shrinkage2

Compassionate care or increased access to marijuana?  < 5%

- Less than 5% of card holders are cancer, HIV/AIDS, or glaucoma patients.
- 90% are registered for ailments such as headaches and soft tissue pain.

Compassionate care or increased access to marijuana?  > 90% card holder not medical use

- Most card holders in CA and CO are white men between the ages of 17 and 35.
- No history of chronic illness.
- History of Alcohol and Drug Use.
Los Angeles has become the medical marijuana capital of the world... more dispensaries than Starbucks cafés.

Is that because we are more compassionate or have more sick people?
Main Phytocannabinoids
(490 chemicals in pot, ~66 are psychoactive)
Three most considered in medical pot:
• THC: Main psychoactive chemical, anti-emetic, appetite stimulant, analgesia
• CBD (cannabidiol): much less psychoactive, anti-seizure, -spasmodic, -emetic, -inflammatory, analgesia, sedating, neuroprotective
• CBN (cannabinol): anti-seizure, -inflammatory, phase II sedative effects
Note: ~2,000 chemicals produced when pot is combusted

THC & CBD often work in opposition to each others effects

THC - Recreational use interests
CBD - Drug Companies Interests

Euphoria No euphoria
Anxiety Anti-anxiety
Psychosis Anti-psychotic
Cognitive impairment No cognitive impairment
Hunger Anti-obesity

CBD medical potentials: reduce atherosclerosis, anti-tumor, Anti-metastasis, Anti-inflammatory, Neuroprotective, Gum protective, Anti-obesity, analgesic, Anti-psychotic, Anti-depressant, Anti-anxiety

But: THC-to-CBD Ratio Continues to Increase

Physiological Effects of Endocannabinoids
Endocannabinoids are often produced as an adaptive response to cellular stress, aimed at reestablishing cell homostasis
Endocannabinoids affect a large number of physiologic processes including
- Feeding behavior
- Energy balance, metabolism, and GI function
- Pain perception
- Motor control and posture
- Learning, memory, and emotions
- Immune and inflammatory responses
- Cardiovascular function
- Reproduction
- Bone formation
Avidekel: marijuana hybrid to increase CBD/THC ratio for medical use
More thoughtful approaches to medical pot:

• Dr. Sanjay Gupta CNN Reports on Colorado R4 Strain = 17.61% CBD/0.76% THC in 2013
• Stanley brothers of Colorado Springs create Charlotte’s Web strain = 17% CBD/<0.03% THC in 2013
• Dr. Manuel Guzman, Complutense Univ. Madrid, Spain CBD/THC/temozomide for brain cancer, 2015

Hawaii Medical Marijuana Laws Limits Use to Debilitating Medical Conditions
1. Cancer, Glaucoma, HIV+, AIDS
2. Medical Condition or a Treatment that produces any of the following:
   a.) Cachexia or Wasting Syndrome
   b.) Severe Pain
   c.) Severe Nausea (2012 C. Hyperemesis Syndrome?)
   d.) Seizures
   e.) Severe and Persistent Muscle Spasms (i.e. Multiple Sclerosis, Crohn's)
3. Others as approved by Health Department

Potential Medical Benefits of Cannabinoids (Not Pot)
Lack of rigorous empirical studies but lots of anecdotal support for utility in treatment of:
• nausea/vomiting esp. from chemotherapy??
• wasting disease, poor appetite??
• restless leg syndrome, dystonias, analgesia
• anxiety, sleep disorders, & depression
• autism, epilepsy, multiple sclerosis
• glaucoma, itching, asthma, chronic pain

Is smoking pot medical marijuana?
NORML medical marijuana outlet in Medford promotes safer less harmful processes:
• “medibles” (edible marijuana products) e.g. cookies, butter, lollipops, candy, ice cream, sorbet, soft drinks, Gel caps
• spray, drop, vaporization inhalation of pot or alcohol extracts for oral or vaporization mist
• marijuana ointment, cream, salve, tincture

Hemp Oils Alleged Cancer Cure Used in Baking, Butter, Salads, Marinades, et al.

Vaporizers
How do vaporizers work?

- When cannabinoids are heated to between 285 °F (140 °C) and 392 °F (200 °C) they literally boil and vaporize.
- Studies show that vaporization is most effective at around 338 °F (170 °C).
- A vaporization temperature over 392 °F (200 °C) will burn the cannabis, creating unwanted smoke.

Juicing Medical Marijuana
No Heating, Non-Psychoactive?

Dronabinol (Marinol)

- Dronabinol is 100% THC, the most psychoactive ingredient in cannabis. Natural cannabis is 20% THC or less.
- The physiological effect of THC is modulated when the other cannabinoid forms are present. Dronabinol is associated with too many psychoactive effects.
- DEA classifies dronabinol as schedule III.
- FDA approved dronabinol for treatment of nausea and vomiting associated with chemotherapy and anorexia associated with weight loss in patients with HIV/AIDS.
- Is dronabinol an appropriate substitute for natural cannabis?
- Dronabinol is very expensive.
- Sativex is much better but not available in US (50% THC, 50% cannabadiol in a sublingual spray)

Medical Synthetic THC
2000's Synthetic Cannabinoids

- dronabinol (Marinol®)
- nabilone (Cesamet®)
- THC + CBD (Sativex®)
- Cannabis Sativa Extract (Sativex®)
- CBD (Epidiolex®) FDA approved 6/20/18 for Dravet, Lennox-Gastaut, Tourettes Seizure Disorder.
Sativex Oromucosal Extract

- 1:1 combination from two clonal cannabis cultivars yielding a high THC extract (Tetranabinex®) and a high CBD extract (Nabidiolex®).
- a botanical drug substance (BDS) of defined composition with controlled reproducibility batch to batch.
- THC and CBD comprise some 70% (w/w) of the total BDS, with minor cannabinoids (5 – 6%), terpenoids (6 – 7%, most GRAS), steroids (6%), triglycerides, alkanes, squalene, tocopherol, caretenoids and other minor components (also GRAS).
- each 100 μL pump-action spray provides 2.7mg of THC and 2.5mg of CBD, the minor components, plus ethanol: propylene glycol excipients, and 0.05% peppermint as flavouring.
- Intermediate onset: 15-40 minutes
- Allows dose titration; Reduces first pass metabolism
- MUCH BETTER THAN MARINOL

Now Medical CBD Liquid for Vaping alleged legal in U.S.

Epidolex® (cannabidiol – GW Pharma Labs) FDA Approved 6/20/18

- Approved for Lennnox-Gastaut and Dravet seizure syndromes
- Warning: On-Line and Dispensary CBD Products inconsistent with purity and labeling: 70% Mislabeled

Recent Interest in CBD to decrease drug cravings especially for Opioid Use Disorder


CLINICAL USES OF CANNABIS IN CHRONIC PAIN

- Neuropathic pain; Myofascial pain
- Sleep, mood, and appetite improvement
- Enhances effects of opioids and helps offset opioid side effects
- Helps with muscle spasms
- No constipation or respiratory suppression
- No LD50

CDC: 153 possible cases of vaping-related illnesses, many involving THC in July & Aug. 2019

- Students drop cigarettes, turn to vaping
- Percentage of middle- and high school students using cigarettes and e-cigarettes each year
- Also, flavored E-Cigarettes (esp. cinnamon) linked to Risk for Cardiovascular Disease
- Hauk, G (2019) USA Today 8/23/19
Cannabinoid Suppression of Neuropathic Pain – Basic Science

• In CCI of infraorbital nerve model, CB1 receptor upregulation was observed in both the ipsilateral and contralateral superficial layer of the trigeminal caudal nucleus (I>C)
• CB2 receptor immunoreactivity is increased in the ipsilateral dorsal horn after L5 spinal nerve transection
• Saphenous partial nerve ligation increased u-opioid, CB1, and CB2 receptor protein levels in ipsilateral/contralateral hind paw skin, DRG, and ipsilateral/contralateral L-cord (17 days post-surgery)
• Tibial nerve injury → upregulation of CB1 receptor mRNA in the contralateral thalamus, 1 day post-surgery
• SCI model—mechanical allodynia was reduced with chronic administration of WIN (mixed CB agonist) with no decrease in effectiveness, unlike morphine

Arguments for Cannabinoid Pain Management

• Analgesia: different mechanism than opiates, some synergy though.
• Spasticity: likely GABA mediated
• Appetite enhancement: hippocampal?
• Anti-emetic: cerebellar? (2012 C. Hyperemesis Syndrome??)
• Elevated levels of the CB1 receptor are found in areas of the brain that modulate nociceptive processing
• CB1 and CB2 agonists have peripheral analgesic actions
• CBs may also exert anti-inflammatory effects
• Analgesic effects not blocked by opioid antagonists

What is the evidence base?

• Medline-Indexed Publications on Cannabis and Cannabinoids: It is estimated that there are now over 15,000 articles on the chemistry and pharmacology of cannabis and cannabinoids and over 2,000 articles on the endocannabinoids in the scientific literature.

In the past 15 years

• There have been 33 completed and published American controlled clinical trials with cannabis
• Compared with placebos or standard drugs, including sometimes dronabinol
• Assessed appetite stimulation, pain in HIV neuropathy and other types of chronic and neuropathic pain, spasticity in multiple sclerosis, weight loss in wasting syndromes, intraocular pressure in glaucoma, dyspnea in asthma, and emesis due to cancer chemotherapy

Cannabinoids have suppressed neuropathic nociception in 9 different animal models

• Chronic constriction injury: infraorbital nerve, saphenous nerve
• Partial nerve ligation: sciatic, saphenous
• Spinal nerve ligation: L5
• Spared nerve injury
• Spinal cord injury
• Tibial nerve injury
• Streptozotocin-induced diabetic neuropathy

47 States and D.C with Medical Pot Laws
2018 & 11
2012 Meta Analysis of National Surveys:
Residents of Med. Pot States have:
• Higher rates of Pot Use
• Higher rates of Pot abuse/dependence
• Much Lower Adolescent Perception of Pot being Harmful and
• Much Higher Adolescent Average Pot Use
As compare to States with no Med. Pot Laws

National Academies of Science, Engineering and Medicine
The Health Effects of Cannabis and Cannabinoids January 12, 2017
Strong Evidence of use to increased risk:
- Schizophrenia & other psychosis
- Driving problems and auto accidents
- ↓ Infant birth weight if used during pregnancy
- ↑ respiratory problems, and chronic bronchitis
- Cannabis Use Disorder (marijuana addiction with withdrawal symptoms and cravings

Some or Limited Evidence use can ↑ risk:
- Depressive disorders but not that it can make it worse or cause PTSD
- Impaired school achievement, ↑ unemployment or harms social functioning
- ↑ of a type of testicular cancer but no risk of lung
  or other types of cancer
- ↑ triggering a heart attack in those at risk for such
- ↑ abuse and dependence to alcohol, tobacco and other illicit drugs

Marijuana (Cannabinoids)
Medication Interactions
Additive Effects
- Antagonism
- Synergism or Potentiating
Drug Interaction Severity Levels

- **MAJOR** – avoid or usually avoid the combination
- **MODERATE** – usually avoid or minimize the risks of the drug combination
- **MINOR** – no interactions yet reported, ok to use combination but discontinue combination if the need arises

Major Marijuana Interactions

- Additive to Synergistic with **All Sedative-Hypnotics**: e.g. barbiturates, benzodiazepines (Ativan®, Xanax®, Klonopin®), Z-Hypnotics (Ambien®, Sonata®, Lunesta®, Imovane®, Rozerem®); increased sedation, dizziness, cog./psychomotor impairment
- Additive with levomethadyl acetate (also methadone and opioids); increased sedation, coma, respiratory depression, hypotension

Phyto and Synthetic Cannabinoids and Cytochrome P450 system

THC and CBD effects on the Cytochrome P450 system (CYP3A4, CYP2D6, CYP2C19, CYP1A2, et al.) This results in usually inhibition of the metabolism system increasing the levels of drugs that are metabolized by the enzymes as well as increasing levels of the cannabinoids used.

Cannabis increases methadone clearance (opposite of benzos)

- Trough plasma methadone concentrations were measured on 77 Australian and 74 Swiss MMT patients with no additional medications other than benzodiazepines. Simple and multiple regression analyses were performed for the primary metric, plasma methadone concentration/dose.
- Cannabis significantly lowered plasma methadone concentrations.
- benzodiazepines significantly raised plasma methadone concentration (competitive inhibition of CYP3A4).

Cannabinoids and the CYP450 Enzyme Systems

<table>
<thead>
<tr>
<th>Metabolizing enzyme</th>
<th>Enzyme inhibition</th>
<th>Enzyme induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoked cannabis</td>
<td>2C9, 2C19, 3A4</td>
<td>3A4, 2B6, 2C9, 2D6</td>
</tr>
<tr>
<td>Tetrahydrocannabinol</td>
<td>2C9, 3A4</td>
<td>3A4</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>2C19, 3A4</td>
<td>2B6, 2C9, 2D6, 3A4</td>
</tr>
<tr>
<td>Nabilone</td>
<td>2C9</td>
<td>—</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>2C9, 3A4</td>
<td>3A4</td>
</tr>
</tbody>
</table>

Fairly well documented with combinations of warfarin and clobazam (Onfi® Antiepileptic medication) resulting in synergistic effects

Balick, R (2018); Geffrey, AL et al. (2015); DOH (2018)

Major Marijuana Interactions

- Antagonistic with theophylline: decreased theophylline’s effects
- Additive to Synergistic with apomorphine (Apokyn®, Urima®, Spontane®, Clobazam-Onfi®); increased sedation, dizziness, cognition & psychomotor impairment BUT
- Antagonistic if apomorphine is being used as an emetic to induce vomiting
- Psychosis when used with lithium
Marijuana Moderate Interactions

- Undefined Interaction with disulfiram (Antabuse®); results in agitation, sleep problems, and irritability
- Undefined Interaction with fluoxetine (Prozac®); results in irritation, anxiety, jitteriness, excitement or hypomania
- Additive with All Anticholinergics (Artane®, Cogentin®, Akineton®, Kemadrin®); drowsiness, dizziness, cog./psychomotor impairment

Marijuana Moderate But Rare Interaction

- Additive to potentiating if enough medication is absorbed into the body with α₂ adrenergic antagonist ophthalmic drops (Alphagan®, Lopidine®, Combigan®); results in sedation, drowsiness, dizziness, etc.

Marijuana Minor Interactions

- Synergistic with warfarin (Coumadin®); results in increased blood thinning effects of warfarin
- Synergistic with CYP450 3A4 inhibitors (Sprycel®, Tykerb®, Prograf®), results in increased marijuana effects e.g. sedation (Grapefruit?)
- Decreases efficacy of protease inhibitors that increases THC concentrations in blood

Marijuana Interactions with Addictive Substances

- Not a gateway drug per se but it is often the first illicit drug used and those who use it are much more likely to become cocaine or heroin addicted.
- Marijuana is an addictive drug
- Use of marijuana by a recovering alcoholic or a drug addict is correlated with a greater incidence of slips and relapses.

Clinically Useful Drug Interactions

- High CBD to THC ratios of cannabis as can occur with the usage of some strains of herbal cannabinoid medicines and certain cannabinoid-based extracts mitigate THCs anxiogenic, dysphoric, and possibly short-term memory interrupting effects
- Evidence suggests cannabinoids can enhance the analgesic activity of co-administered opioids and the dose of opioids can be therefore be reduced

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction with THC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>THC can increase the effect of fluoxetine.</td>
</tr>
<tr>
<td>TCA</td>
<td>THC can increase the side effects of amtriptyline (i.e. tachycardia, hypertension and sedation).</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Indomethacin and acetylsalicylic acid (aspirin) reduce the effects of THC.</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>These increase the depressive effects of THC and also increase tachycardia associated with THC consumption.</td>
</tr>
<tr>
<td>BZDPS</td>
<td>These drugs can increase depression of the nervous system and also of the respiratory system.</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>These reduce tachycardia associated with THC.</td>
</tr>
<tr>
<td>ETOH</td>
<td>This can increase nervous system deterioration.</td>
</tr>
<tr>
<td>Opioids</td>
<td>Increased sedation and analgesia.</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Cannabinoids increase theophylline catabolism. A dosage increase is thus required in such cases.</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Atropine and scopolamine can increase tachycardia produced by THC.</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>THC interacts with disulfiram, causing a very unpleasant reaction in the patient. The combination of both substances should therefore be avoided.</td>
</tr>
</tbody>
</table>
Dronabinol Product Insert

- In studies…MARINOL Capsules has [sic] been co-administered with a variety of medications (e.g., cytotoxic agents, anti-infective agents, sedatives, or opioid analgesics) without resulting in any clinically significant drug/drug interactions …cannabinoids may interact with other medications through both metabolic and pharmacodynamic mechanisms. Dronabinol is highly protein bound to plasma proteins, and therefore, might displace other protein bound drugs. Although this displacement has not been confirmed in vivo...

ng/ml RIA Value to Use Pattern

- > 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

Issues Involved with Marijuana Urine Drug Screen (UDS)

Second hand exposure controversy

Secondhand exposure controversy: 6 experienced user smoked in same room with 6 non users first at 50 ng/mL in a non 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 Analysis (UA) Complications

- 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)

Urine Creatinine

- 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 daily basis.

Increased fluids lower 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.

Conclusion: Marijuana is a Drug with both useful and harmful effects like all others

<table>
<thead>
<tr>
<th>SUBSTANCE</th>
<th>DRUG</th>
<th>MEDICAL USES</th>
<th>ADDICTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>nicotine</td>
<td>some</td>
<td>yes</td>
</tr>
<tr>
<td>Booze</td>
<td>ethanol</td>
<td>limited</td>
<td>yes</td>
</tr>
<tr>
<td>Opium</td>
<td>opioids</td>
<td>vital uses</td>
<td>yes</td>
</tr>
<tr>
<td>E. Coca</td>
<td>cocaine</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Marijuana</td>
<td>THC</td>
<td>potential</td>
<td>yes</td>
</tr>
</tbody>
</table>

Questions?

Conclusion

Conclusion: Marijuana is a Drug with both useful and harmful effects like all others

Marijuana has Positives and Negatives like all drugs

Marijuana is the most commonly used illicit drug in the U.S. & most often listed by all addicts.

Marijuana use begins in adolescence – the most vulnerable brain.

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.
CONCLUSION: Our current political climate of medical, recreational, economic, edible, higher potency marijuana, extracts and synthetics present daunting challenges for all, especially for the extraordinarily vulnerable adolescent brain.

Conclusions
◆ Keeping up on the exploding science of understanding marijuana is daunting, exhaustingly complex and steeped in deep controversy
◆ The Takeaways: Marijuana is a substance that contains many biological active drugs and It is addicting

Thank You!

PowerPoint available at:
www.cnsproductions.com

Darryl Inaba, PharmD., CATC-V, CADC III