



Marijuana and the Developing Brain: What Today's Parents Need to Know

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1



Dangerous Drug Use Trends In America: Marijuana


2




CANNABIS RESEARCH AND POLICY: IMPLICATIONS FOR PUBLIC HEALTH

CANNABIS FORUM
TAADAS, JULY 16, 2021

Susan R.B. Weiss
Director
Division of Extramural Research
National Institute on Drug Abuse



National Institute on Drug Abuse



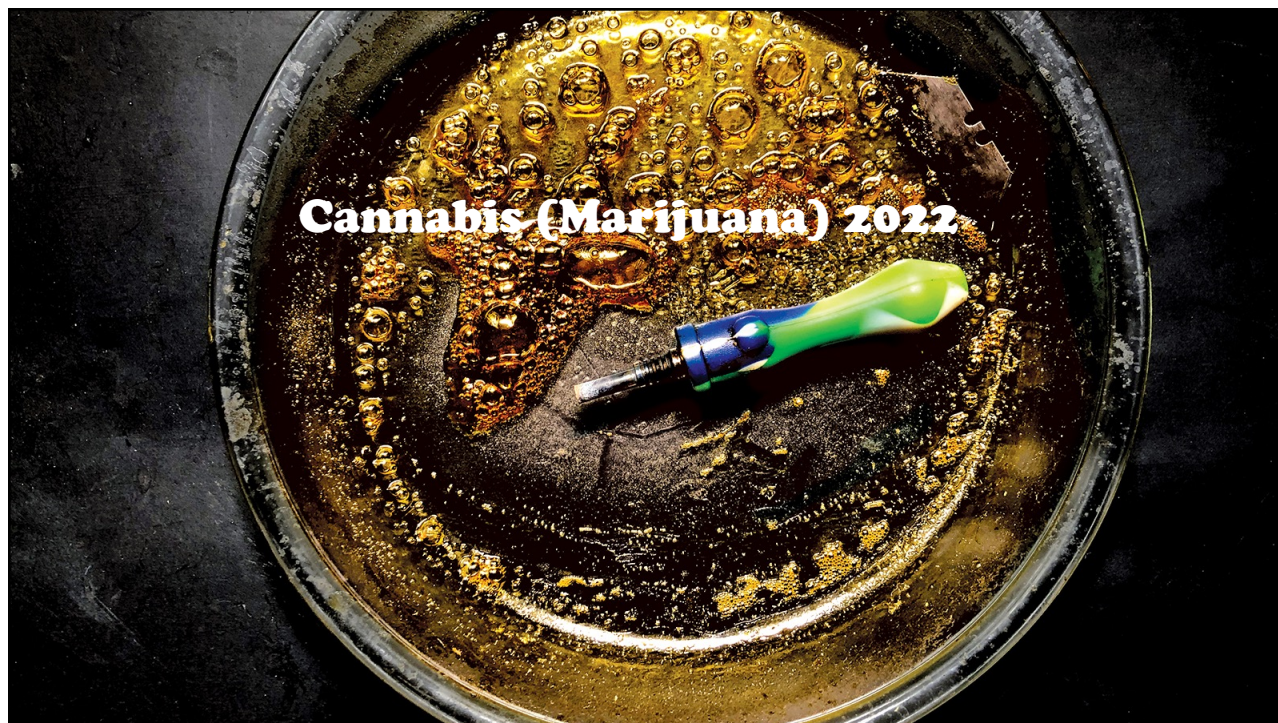
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T.H.C.
TETRAHYDROCANNABINOL

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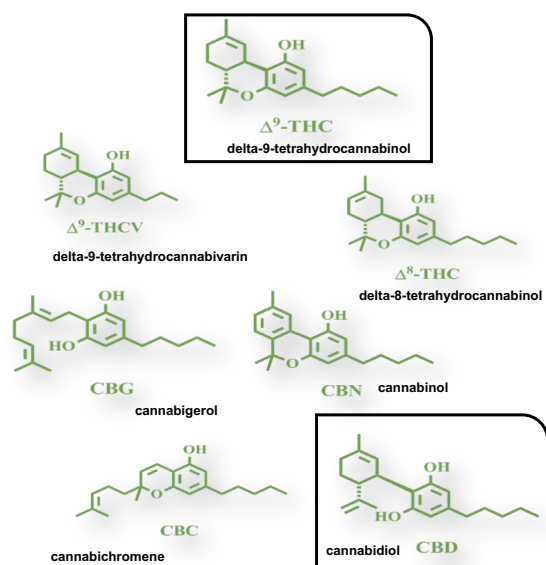


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5

CANNABIS CONTAINS >120 CANNABINOIDS



- *Illegal* under US Federal law (Schedule I substance)
- *Legal for medical use* in 36 States + D.C.
- *Legal for adult use* in 18 States + D.C.
- Low THC products *legal for medical use* in 11 States
- *CBD from Hemp* (defined as cannabis sativa <0.3% THC) no longer falls under the Controlled Substances Act (CSA)
- Versions of *active ingredients* approved (or in clinical trials) for medical indications in U.S. and other countries
 - Synthetic - Marinol, Syndros, Cesamet
 - Plant Derived- Sativex (THC/CBD)
 - Plant Derived-Epidiolex (CBD: FDA No longer scheduled)



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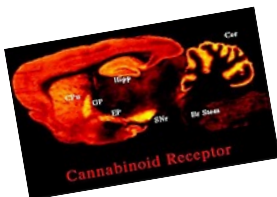
MARIJUANA'S ACUTE EFFECTS: INTOXICATION PHASE

- Euphoria
- Appetite stimulation
- Altered perception of time
- Heightened sensation
- Impaired coordination and balance
- Increased heart rate: 20 - 100%
 - Some evidence for increased risk of heart attack, strokes
- Increased risk of accidents (~2 fold), higher when combined with alcohol
- Cognition
 - Impaired short-term memory
 - Difficulty with complex tasks
 - Difficulty learning
- Executive Function
 - Impaired decision-making
 - Increased risky behavior
- Mood (especially after high doses or edibles)
 - Anxiety – panic attacks
 - Psychosis – paranoia



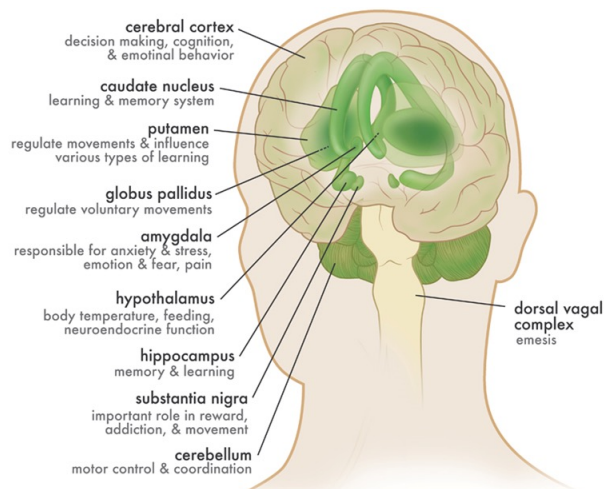
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CANNABINOID RECEPTORS ARE LOCATED THROUGHOUT THE BRAIN



Regulation of:

- Brain Development
- Memory & Cognition
- Movement Coordination
- Pain Regulation & Analgesia
- Immune Function
- Appetite
- Motivational Systems & Reward

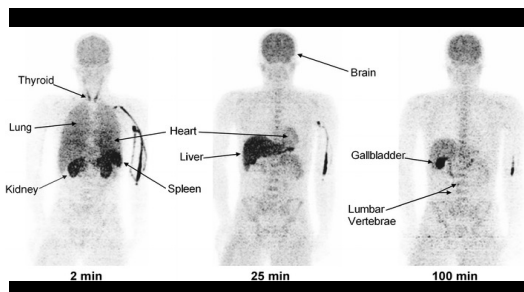


Canadian Consortium for the Investigation of Cannabinoids, <http://www.ccic.net/>

8

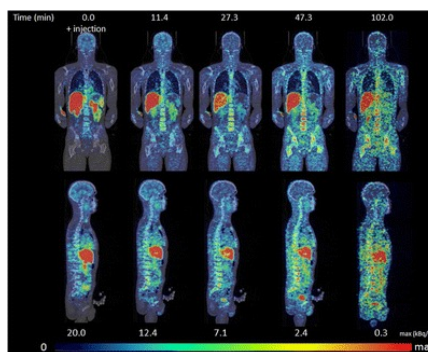
CANNABINOID RECEPTORS ARE ALSO LOCATED THROUGHOUT THE BODY

Whole Body Distribution of CB1 Receptors (2, 25, and 100 min after injection of ¹¹C-MePPEP)



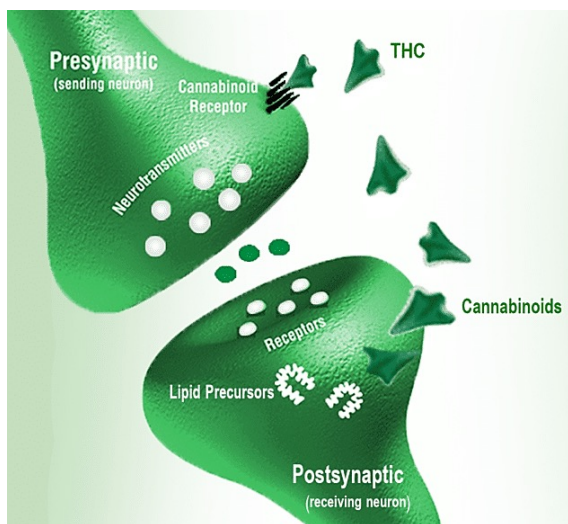
al., Eur J Nucl Med Mol Imaging. 2010

PET images of [¹¹C]-NE40 (CB2R radioligand)



Ahmad et al., Mol Imaging Biol. 2013 A

9



ENDOCANNABINOID SYSTEM

Endocannabinoids are produced *on demand*. They travel back to the transmitting neuron to dampen further activity.

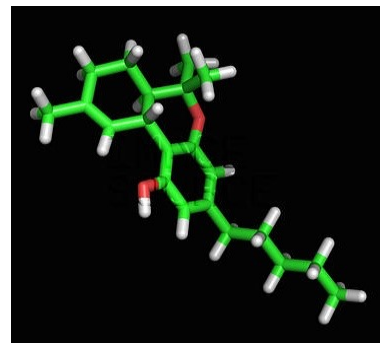
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MARIJUANA: MOST COMMONLY USED "FEDERALLY" ILLICIT DRUG IN THE U.S.

Almost **32 million** Americans 12 and older report past month use.

Approximately **4.8 million** Americans met criteria for cannabis use disorders in 2019.

An estimated **3.5 million** Americans used cannabis for the first time; **1.4 million** were between the ages of 12 and 17.

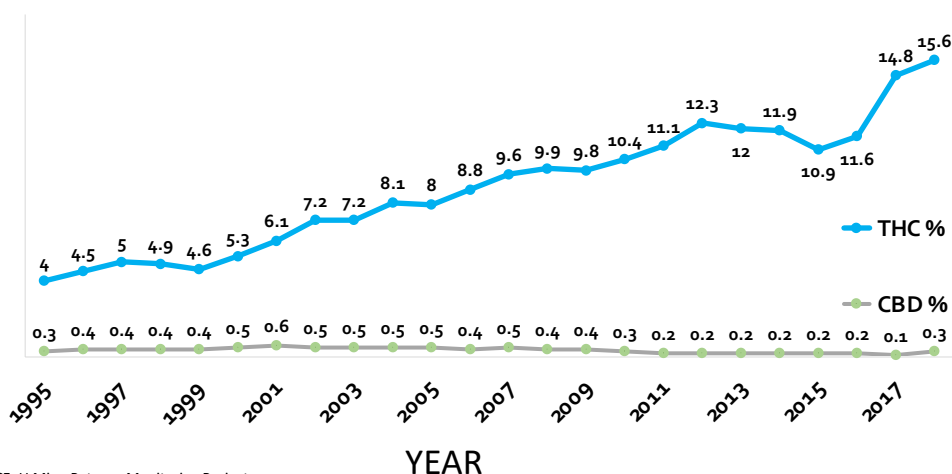


Tetrahydrocannabinol (THC)
Psychoactive Ingredient in Marijuana

2019 National Survey on Drug Use and Health, SAMHSA

11

CHANGING LANDSCAPE: INCREASING POTENCY (%THC), NEW ROUTES OF ADMINISTRATION, CBD PRODUCTS



SOURCE: U Miss, Potency Monitoring Project



12

High-THC Cannabis Concentrates and Their (Scary) Effects on the Teenage Brain

- 5280 Denver's Mile High Magazine
- Lindsay B. King
- *This story won a [2022 National Magazine Award](#) in the Service Journalism category from the American Society of Magazine Editors.*
- *After 5280's July issue went to press, Governor Jared Polis signed into law HB 21-1317, which requires further study of the possible health effects of high-THC cannabis and aims to reduce access to cannabis among teenagers. This article has been updated to reflect the new law.*

13

Know the Lingo

- **Concentrates:** Broadly refers to any cannabis product that has been made through a process where extraneous plant matter is mostly removed, leaving behind only aromatic oils called terpenes and cannabinoids, like cannabidiol (CBD) and THC
- **Dabbing:** The method of flash-vaporizing cannabis concentrates—typically extracted oils of varying consistencies—on a hot surface and inhaling them to get high
- **Dab rig:** Also called an oil rig, this is a water pipe—essentially, a sophisticated glass bong—that has attachments specifically designed for dabs of marijuana concentrate
- **Dabber:** Sometimes called a wand, this is a small tool used to pick up a dab of concentrate and place it on the heated surface of a dab rig
- **Vape pens:** Much like e-cigarettes, these are portable, pen-shaped vaporizers that are typically refillable with cartridges of concentrates
- **Dabs:** A catch-all word for any concentrate or extract that can be flash-vaporized and inhaled
- **E-nail:** A dabbing device that electronically heats the nail
- **Extracts:** A specific type of concentrate made using solvents, like alcohol, butane, propane, or CO₂; all extracts are concentrates, but not all concentrates are extracts
- **Hash:** A pressed cannabis concentrate—made without using solvents—of the plant's sticky glands that is commonly smoked and vaped but can also be dabbed
- **Nail:** The metal, glass, or ceramic spike attached to a water pipe; dabs are applied to the nail once it has been heated up electronically or with a torch
- **Torch:** A handheld butane or propane torch often used to heat the nail of a dab rig; a jet lighter also works
- *King, LB, High-THC Cannabis Concentrates and Their (Scary) Effects on the Teenage Brain, 5280, July 2021*

14

Types of Cannabis Concentrates 2022



15

THC Concentrates

- Shatter**
 An amber-colored extract that has a transparent, stiff, glasslike quality and breaks easily
Typically used with: a dab rig
- Sugar**
 An extract that comes in a wide range of colors—very light yellow to almost amber—and has the consistency of wet, sappy sugar
Typically used with: a dab rig
- Budder**
 A dark yellow extract that has a creamy, butterlike texture
Typically used with: a dab rig
- Live Rosin**
 A high-quality solventless extract, usually pale yellow to golden in color with a goeey, honeylike consistency
Typically used with: a dab rig, a glass bowl, a joint, or a concentrates vape pen
- Crumble**
 An extract that can be yellow, orange, or light brown and that has a soft, crumbly texture
Typically used with: a dab rig or sprinkled over flower in joints, pipes, and bongs
- Wax**
 An extract that has a soft, waxy consistency
Typically used with: a dab rig or a concentrates vape pen
- Distillate**
 A potent cannabis oil extract that has been stripped of all materials and compounds except for certain cannabinoids, like THC or CBD
Typically used with: a concentrates vape pen (with refillable cartridges)
- King, LB, High-THC Cannabis Concentrates and Their (Scary) Effects on the Teenage Brain, 5280, July 2021*

16

Parent Awareness Is Important

Just because you *think* your teenagers don't have the wherewithal to buy concentrates—much less a dab rig—doesn't mean they can't improvise ways to do both.

If you've been finding soda cans or water bottles cut in half; if you're missing butter knives from your drawers; if you've found unwound paperclips; if you can't find your crème brûlée torch...your 15-year-old might be more resourceful than you realize.

All of these items can be used to fashion a homemade dab rig.

Parent awareness is extremely important!!!!

17

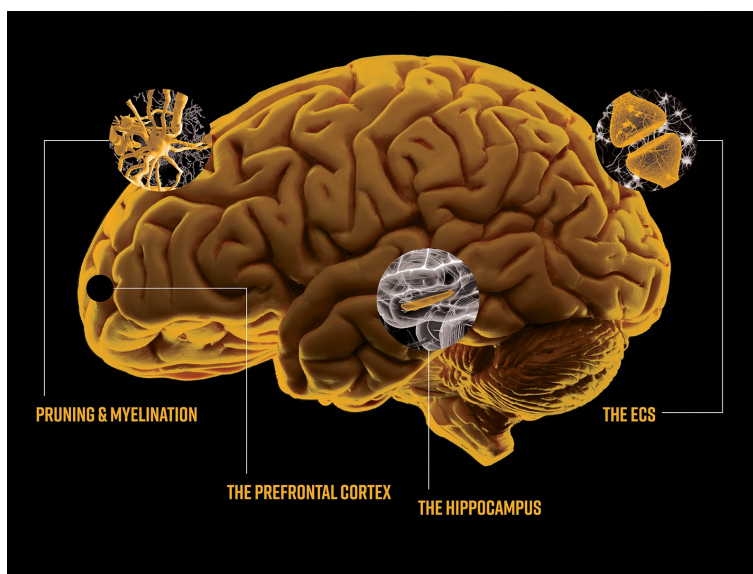
Use of Marijuana: Effect on Brain Health

A Review

- According to the 2002 to 2019 National Survey on Drug Use and Health, the proportion of the US population >12 years of age who used marijuana in the past year increased gradually from **11% in 2002 to 18% in 2019**.
- The potency of cannabis products in the United States, measured by the concentration of the primary psychoactive constituent of marijuana, Δ 9-tetrahydrocannabinol (THC), has **gradually increased from \approx 4% in 1995 to 15% in 2018**.
- **Cannabinoid receptors are expressed in high density in areas of the brain involved in executive function and memory such as the hippocampus, amygdala, and pre- frontal cortex (PFC), particularly during periods of active brain development.**
- *Testai et al, Effect of Marijuana on Brain Health and Cognition, Stroke. 2022;53:e176–e187. DOI: 10.1161/STR.0000000000000396 April 2022*

18

THC Alters Development Changes on Adolescent Brain: Delayed Neural Enhancements



19

INSIDE THE ADOLESCENT BRAIN

The brain undergoes two major developmental spurts, one in the womb and the second from childhood through the teen years, when the organ matures by fits and starts in a sequence that moves from the back of the brain to the front.

Corpus Callosum
 Though it has stretched to meet the brain's increased size, the corpus callosum, the bridge of nerve fibers that connects the left and right halves of the brain, is still growing. The nerve fibers in the corpus callosum are still being produced and are still being myelinated.

Prefrontal Cortex
 The prefrontal cortex, the part of the brain that is responsible for planning, decision-making, and impulse control, is still developing. It is the last part of the brain to mature, and it is still being myelinated.

Basal Ganglia
 Large, irregularly shaped masses of gray matter, the basal ganglia are part of the brain's motor system. They are still developing and are still being myelinated.

Myelination
 The process of myelination, the coating of nerve fibers with a protective sheath of myelin, is still ongoing. It is the last part of the brain to mature, and it is still being myelinated.

Nerve Proliferation ...

Slide courtesy of Ken Winters, PhD.

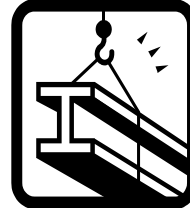
What We Now Know

- Adolescence is a **critical period** in brain development.
- The brain is still developing until approximately age 24 or 25

20

20

Construction Ahead



BLOSSOMING:

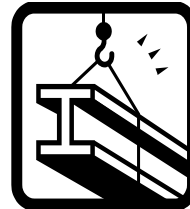
Until about ages 10-12, the brain undergoes rapid growth, including:

- Neuron numbers increasing
- Neurons getting bushier
- Neuron connections increasing

21

21

Construction Ahead

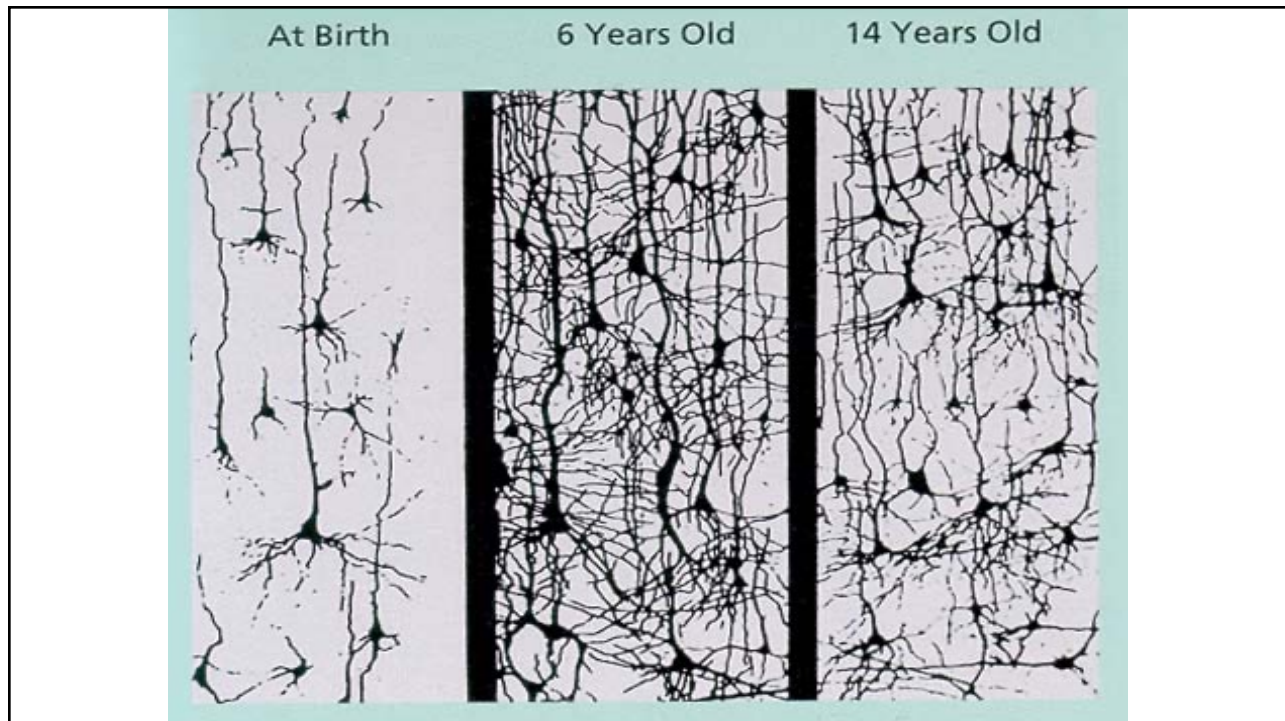


Around age 12, neuronal growth starts to undergo **pruning**, following the principle of “use it or lose it.”

Slide courtesy of Ken Winters, PhD.

22

22



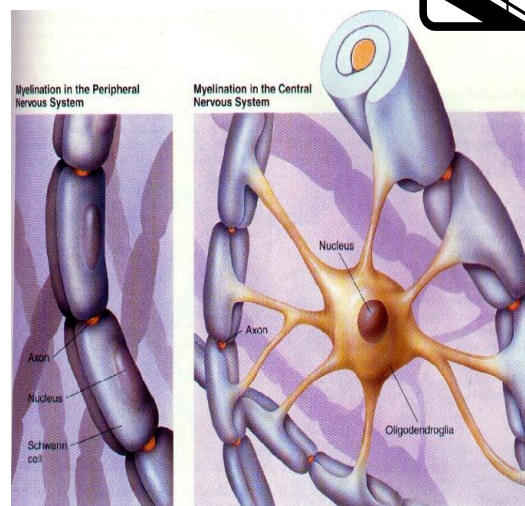
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Construction Ahead



Along with pruning, **myelin** starts to cover axons and then thicken.

The myelin sheaths help action potential travel **100 times faster.**

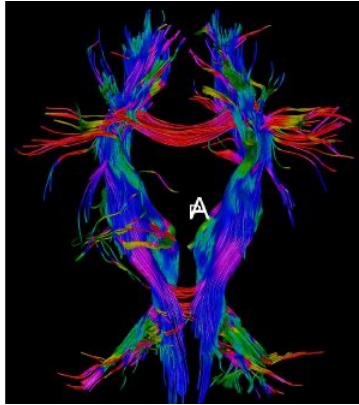


Slide courtesy of Ken Winters, PhD.

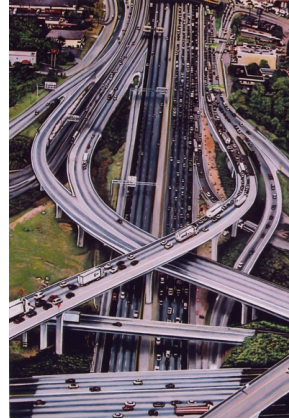
24

24

The Brain's Info Superhighway: Myelinated axons = White Matter Tracts



Source: Gordon J. Harris, PhD.



25

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Construction Ahead



Result of Pruning and Myelination:

Fewer but faster
connections
in the brain.

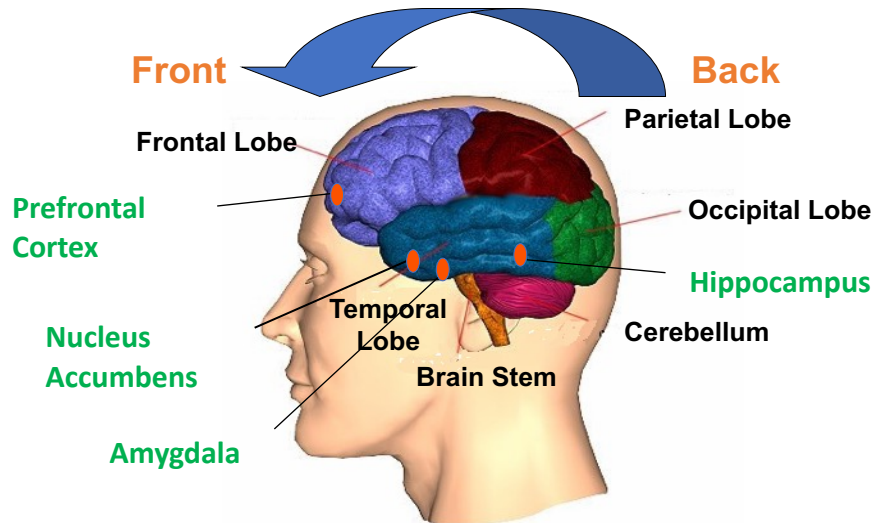


Slide courtesy of Ken Winters, PhD.

26

26

How the Brain Develops



27

27

Brain Maturation



Nucleus Accumbens (highly active in adolescence)

- Pleasure center
- Active during pleasurable activities, including feeding, sex, and drug use
- Plays a major role in addiction



Prefrontal Cortex (matures late adolescence or early adulthood)

- Impulse control
- Decision-making
- Organizing and planning
- Abstract thought, rational thinking
- Attention, focus
- Working memory



28

Windows of Vulnerability of THC Exposure

Abnormal Stress
Responsivity

Glial Cell Activation

Desynchronization of
PFC Neuronal
Networks

Dysfunction in
Excitatory/Inhibitory
Balance

Excessive Synaptic
Pruning

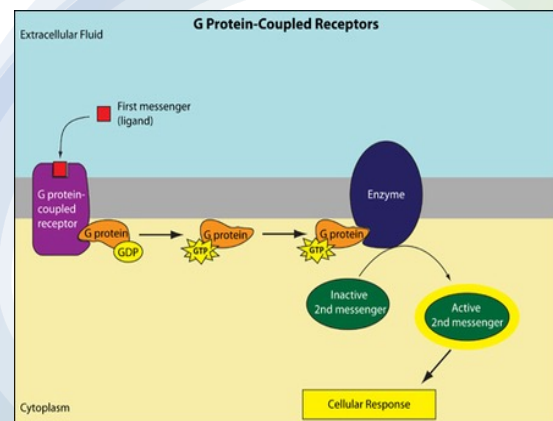
Dysregulation of
monoaminergic
Pathways

Testai et al, Effect of Marijuana on Brain Health and Cognition, Stroke. 2022;53:e176–e187. DOI: 10.1161/STR.0000000000000396 April 2022

29

Types of Receptors

- **CB1:**
 - regulation of neurotransmitter release
 - the heart
 - vascular smooth muscles and endothelial cells
- **CB2:**
 - in the immune cells
 - hematopoietic cells
- **GPR55, PPAR γ**
 - Regulation of neuronal excitability
 - Cell proliferation



30

Abnormal Stress Responsivity

- Synthetic THC and high potency THC products bind to cannabinoid receptors with high affinity and can cause hallucinations, agitation, psychosis, short-term memory loss, seizures, coagulopathy, and myocardial infarction.
- Fernando D. Testai. Stroke. Use of Marijuana: Effect on Brain Health: A Scientific Statement From the American Heart Association, Volume: 53, Issue: 4, Pages: e176-e187, DOI: (10.1161/STR.0000000000000396)

31

Glial Cell Activation

- Glial cells among many other functions they undertake to capture glucose from the blood stream to provide energy and allow the necessary neuronal activity to take place, and thus ensure that cognitive functions are performed correctly.
- Although incompletely understood, the way in which THC disrupts memory and learning may be through its differential effect on neurotransmitter release and binding to CB1 receptors.
- Dr. Pedro Grandes states that THC activates the CB1 receptor in the cellular mitochondria which hampers the metabolism of glucose and the production of lactate in the brain by reducing oxygen –thus a reduction on neural functioning.
- Jimenez-Blasco, D., *et al.* (2020) Glucose metabolism links astroglial mitochondria to cannabinoid effects. *Nature*. doi.org/10.1038/s41586-020-2470-y.

32

Desynchronization of PFC Neuronal Networks

- THC disrupts endocannabinoid signaling pathways and affects synaptic plasticity. In the short term, this affects the strength of interneuronal connections; in the long term, it leads to changes in the functioning of neuronal networks.
- Exposure to THC during adolescence can lead to structural, molecular, and functional alterations of brain circuits, particularly in areas involved in cognition and behavior.
- Fernando D. Testai. Stroke. Use of Marijuana: Effect on Brain Health: A Scientific Statement From the American Heart Association, Volume: 53, Issue: 4, Pages: e176-e187, DOI: (10.1161/STR.0000000000000396)

33

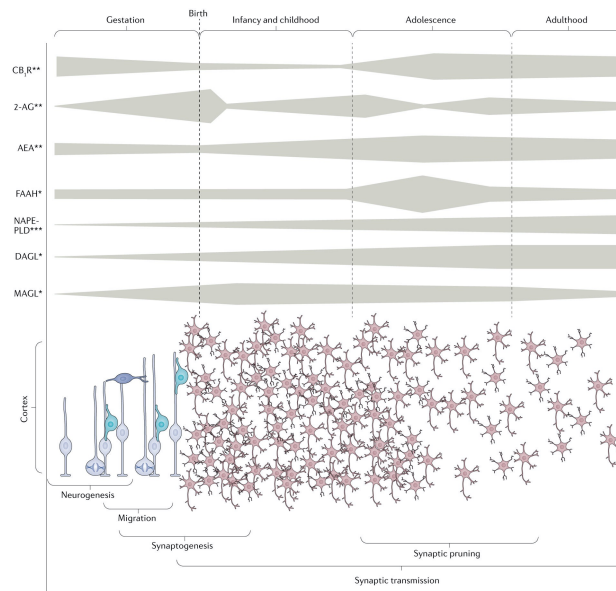
Dysfunction in Excitatory/Inhibitory Balance

- Changes in the balance of excitatory and inhibitory input strength, along with alterations in how principal neurons and interneurons receive, integrate, and convey information, have been observed in these neuroanatomic areas.
- Changes in glutamate and GABA may create the risk for increased anxiety and depression in adolescents.
- Fernando D. Testai. Stroke. Use of Marijuana: Effect on Brain Health: A Scientific Statement From the American Heart Association, Volume: 53, Issue: 4, Pages: e176-e187, DOI: (10.1161/STR.0000000000000396)

34

Excessive Synaptic Pruning
Nat Rev Neurosci. Author
manuscript; available in PMC 2021
September 16, 2021

Excessive synaptic pruning may be the
reason for psychotic episodes with high
dose THC

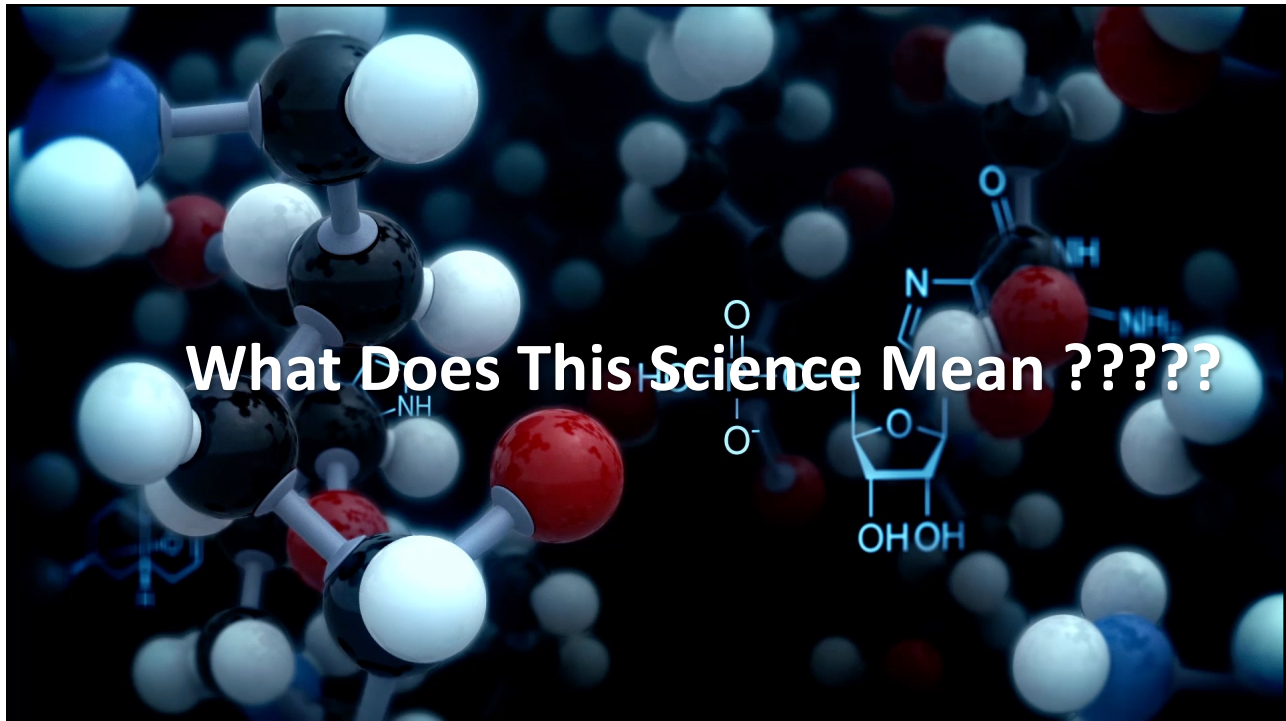


35

Dysregulation of Dopamine Pathways

- THC produces complex effects on the dopamine system, contributing to the drug's recreational and harmful effects.
- Low doses of THC produced increases in the conversion of tyrosine to dopamine, but high doses of THC resulted in decreased dopamine synthesis.
- There is also evidence of reduced dopamine transporter (DAT) density in chronic cannabis users.
- Human PET studies have demonstrated blunted dopamine synthesis and dopamine release in cannabis users relative to non-users, yet we still need to understand the precise mechanisms through which this occurs.
- Long Term use may worsen depression and create anhedonia
- Bloomfield MA, Ashok AH, Volkow ND, Howes OD. The effects of Δ^9 -tetrahydrocannabinol on the dopamine system. *Nature*. 2016;539(7629):369-377. doi:10.1038/nature20153

36



37

Physiologic Effects of Cannabis Use

- ***Acute Intoxication***
- Slowed reaction times and impaired motor coordination
- Impaired attention, concentration, short-term memory, and risk assessment
- Distortions in time and spatial perception
- Increased intensity of visual/auditory perception
- Depersonalization, hallucination, grandiosity, paranoia, and/or other signs of psychosis
- Kalensky, M., *The Pros and Cons of Medical Cannabis: Current Evidence*, *The Clinical Advisor*, Nov 11, 2021

38

Physiologic Effects of Cannabis Use

Cardiovascular Effects

- Dose-dependent increases in heart rate and blood pressure can occur with acute intoxication.
- Orthostatic hypotension is a common side effect in older adults.¹⁴ Other potential physiologic changes can include increased platelet aggregation, arterial vasospasm, and increased cerebral vascular tone, which can result in decreased cerebrovascular blood flow.
- In the hours after ingestion, cannabis increases the risk for major cardiovascular events, such as hypertensive emergency, myocardial infarction, transient ischemic attack, and cerebrovascular accident.
- Chronic use in individuals with a history of angina may lower the angina threshold and, thus, precipitate chest pain.
- There also is evidence to suggest a link to new cardiac arrhythmia secondary to ischemia.
- Atrial fibrillation, ventricular fibrillation, and Brugada pattern (ventricular arrhythmia) are the most commonly associated arrhythmias; when such arrhythmias occur, the mortality rate is estimated at 11%.
- Kalensky, M., *The Pros and Cons of Medical Cannabis: Current Evidence*, *The Clinical Advisor*, Nov 11, 2021

39

Physiologic Effects of Cannabis Use

Pulmonary Effects

- Inhalation of cannabis and associated respiratory irritants can cause acute or chronic cough, increased mucous production, and shortness of breath.
- Pneumomediastinum can be an acute complication associated with holding one's breath in during inhalation.
- Evidence suggests that long-term cannabis use may lead to large airway inflammation, increased airway resistance, and lung hyperinflation.
- In individuals with underlying pulmonary disease, such as asthma or chronic obstructive pulmonary disease (COPD), this may increase the risk for respiratory infection and acute exacerbations of chronic disease.
- Kalensky, M., *The Pros and Cons of Medical Cannabis: Current Evidence*, *The Clinical Advisor*, Nov 11, 2021

40

Physiologic Effects of Cannabis Use

- **Prolonged Neuropsychiatric Effects**
- Cannabis use in children has the potential to alter brain development and can be linked to poor educational outcomes, such as increased drop-out rates.
- Use in adolescents is correlated with cognitive impairment and lower IQ scores.
- In adults, use causes memory impairment and difficulty learning new information.
- In some individuals, cannabis increases the risk of developing or worsening of depression, anxiety, and post-traumatic stress disorder.
- Cannabis use is linked with the development of psychosis, particularly among youth who have preexisting genetic vulnerability, and may advance onset of first psychotic episode by 2 to 6 years in such individuals.
- Long-term use has been linked with the development of amotivational syndrome and reports of decreased life satisfaction.¹⁸
- Kalensky, M., *The Pros and Cons of Medical Cannabis: Current Evidence*, *The Clinical Advisor*, Nov 11, 2021

41

Physiologic Effects of Cannabis Use

- **Cannabis Hyperemesis Syndrome**
- Patients typically present with intense and unremitting abdominal pain with persistent nausea and vomiting, often with reports of multiple episodes over months to years.
- Clinical history reveals a heavy use of cannabis daily over a prolonged period of time.
- Often patients report the only effective alleviating factor for associated abdominal pain is the use of hot baths or showers.
- Generally, symptom presentation occurs in 3 phases: *prodromal*, acute nausea and diffuse abdominal pain, the intensity of which often causes fear of vomiting; *hyperemetic*, multiple episodes of vomiting, driving the patient to seek medical care; and *recovery*, during which normal eating patterns resume.¹⁹
- Kalensky, M., *The Pros and Cons of Medical Cannabis: Current Evidence*, *The Clinical Advisor*, Nov 11, 2021

42

Physiologic Effects of Cannabis Use

- **Use in Pregnancy and Breastfeeding**
- Minimal data exist on the safety and effects of cannabis use in pregnancy. Both the American College of Obstetrics and Gynecology and the American Academy of Pediatrics advise against cannabis use during pregnancy and breastfeeding, citing concern for adverse neurodevelopmental effects.
- Some psychoactive components of cannabis likely cross the placental barrier, with fetal plasma concentrations estimated to be 10% to 30% of maternal serum concentrations.
- With the highly lipophilic nature of THC, it is important to counsel patients that fetal exposure may occur for 4 to 6 weeks after maternal cessation
- Based on the available evidence, complications of use during pregnancy may include higher rates of maternal anemia, up to twice the rate of preterm births, reduced birth weight, increased likelihood of neonatal intensive care unit stays, and learning/attention deficits into childhood.
- Studies suggest that THC accumulates in breast milk. Peak levels occur approximately 4 hours after maternal inhalation and detectable levels persist for at least 6 days after last maternal use.
- Lack of federal regulation in cannabis supply and distribution also raises concern for the potential secondary exposure to pesticides, heavy metals, bacteria, and fungi through cannabis use
- Kalensky, M., *The Pros and Cons of Medical Cannabis: Current Evidence*, *The Clinical Advisor*, Nov 11, 2021

43

New Research on Marijuana's Impact on Adolescents

- **In March 2021**, *JAMA Pediatrics* published the results of an [addiction study executed by National Institute on Drug Abuse](#) scientists.
- The research examined the proportion of adolescents and young adults who had developed substance use disorders (SUDs) in the previous year at various intervals since they first used certain drugs, including cannabis. The findings?
- **Marijuana users between 12 and 17 had nearly double the prevalence (10.7 percent) of SUDs one year after first using cannabis compared with adolescents who first used alcohol (5.6 percent) or nicotine (6.6 percent).**
- **After three years, the addiction rate for cannabis among adolescents was 20.1 percent; it was 10.9 percent for those ages 18 to 25.**
- The data, says the National Institutes of Health, emphasize the vulnerability of young teenagers to developing SUDs
- **ND Volkow, et al. *Prevalence of Substance Use Disorders by Time Since First Substance Use Among Young People in the US*. *JAMA Pediatrics* DOI: 10.1001/jamapediatrics.2020.6981 (2021).**

44

New Research on Marijuana's Impact on Adolescents

- **A mostly Europe-based study** that aimed to identify patterns of cannabis use with the strongest effect on developing psychotic disorders received a lot of attention when it was [published in the Lancet](#) in March 2019.
- The conclusions were disturbing.
- **Daily cannabis use was associated with higher likelihoods of psychotic disorders compared with people who had never used marijuana, but those numbers rose to nearly five times increased odds for daily use of high-THC types of cannabis.**
- **Another disconcerting finding:** Those who had started using high-concentration cannabis by age 15 showed a doubling of risk of psychotic disorders compared with those who had never used.

45

EFFECTS OF MARIJUANA USE ON CEREBROVASCULAR RISK AND DISEASE

- **With marijuana use, the most common acute reaction in humans is a decrease in blood pressure resulting from cannabinoid effects on the vasculature and autonomic nervous system.**
- **The relationship between marijuana use and elevated blood pressure, especially among heavy users, may drive longer-term associations with cerebrovascular outcomes, although this mechanism remains to be studied.**
- **Risk of MI was elevated 4.8-fold within an hour after smoking marijuana compared with periods of nonuse.**
- **A Nationwide Inpatient Sample study found that cannabis use among men and women hospitalized between 2004 and 2011 was associated with a 17% increased relative risk for acute ischemic stroke in a multivariable-adjusted analysis.**
- *Testai et al, Effect of Marijuana on Brain Health and Cognition, Stroke. 2022;53:e176–e187. DOI: 10.1161/STR.000000000000396 April 2022*

46



The Neuroscience of THC

6/19/22

Dr. Merrill Norton, Pharm.D., D.Ph., CMAC

47

47

51 Medical Conditions For Which Marijuana Is Approved by a State

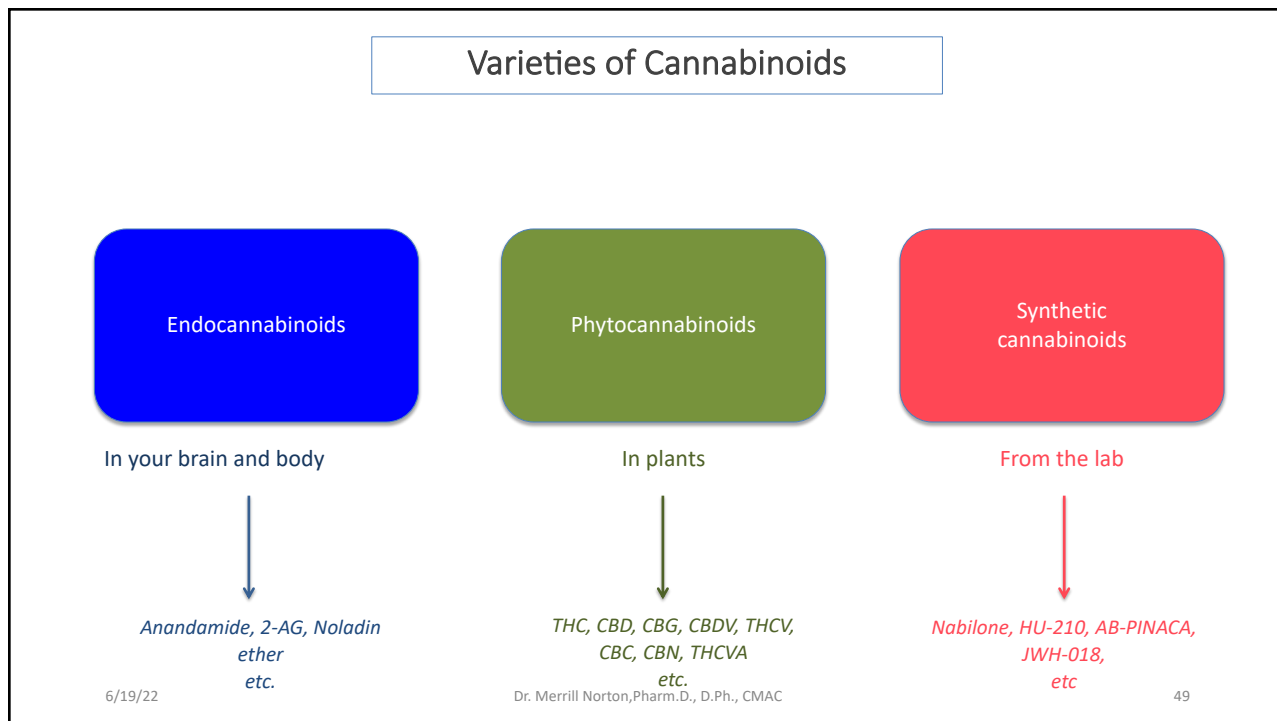
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|---|--|
| 1. Alzheimer's Disease | 26. Lupus |
| 2. Anorexia | 27. Migraines |
| 3. Arnold-Chiari malformation | 28. Multiple Sclerosis |
| 4. Arthritis | 29. Muscle spasms |
| 5. Ataxia | 30. Muscular dystrophy |
| 6. Cachexia | 31. Myasthenia gravis |
| 7. Cancer | 32. Myoclonus |
| 8. Cardiopulmonary respiratory syndrome | 33. Nail-patella syndrome |
| 9. Causalgia | 34. Nausea or vomiting |
| 10. Cervical dystonia | 35. Neurofibromatosis |
| 11. Crohn's disease | 36. Neuropathy |
| 12. Decompensated cirrhosis | 37. Pain |
| 13. Dystonia | 38. Pancreatitis |
| 14. Epilepsy | 39. Parkinson's disease |
| 15. Fibromyalgia | 40. Peripheral neuropathy |
| 16. Glaucoma | 41. Post-traumatic stress disorder (PTSD) |
| 17. Hepatitis C | 42. Reflex sympathetic dystrophy |
| 18. HIV/AIDS | 43. Residual limb pain from amputation |
| 19. Huntington's disease | 44. Seizure disorders |
| 20. Hydrocephalus | 45. Sjogren's syndrome |
| 21. Inflammatory autoimmune-mediated arthritis | 46. Spasticity |
| 22. Inflammatory bowel disease (IBS) | 47. Spinal cord damage with intractable spasticity |
| 23. Inflammatory demyelinating polyneuropathy | 48. Syringomyelia |
| 24. Interstitial cystitis | 49. Terminal illness |
| 25. Lou Gehrig's disease (amyotrophic lateral sclerosis, ALS) | 50. Tourette's syndrome |
| | 51. Traumatic brain injury |

Sources: Marijuana Policy Project, 2014. Key Aspects of State and D.C. Medical Marijuana Laws, from National Conference of State Legislatures, "State Medical Marijuana Laws," www.ncsl.org/; 22
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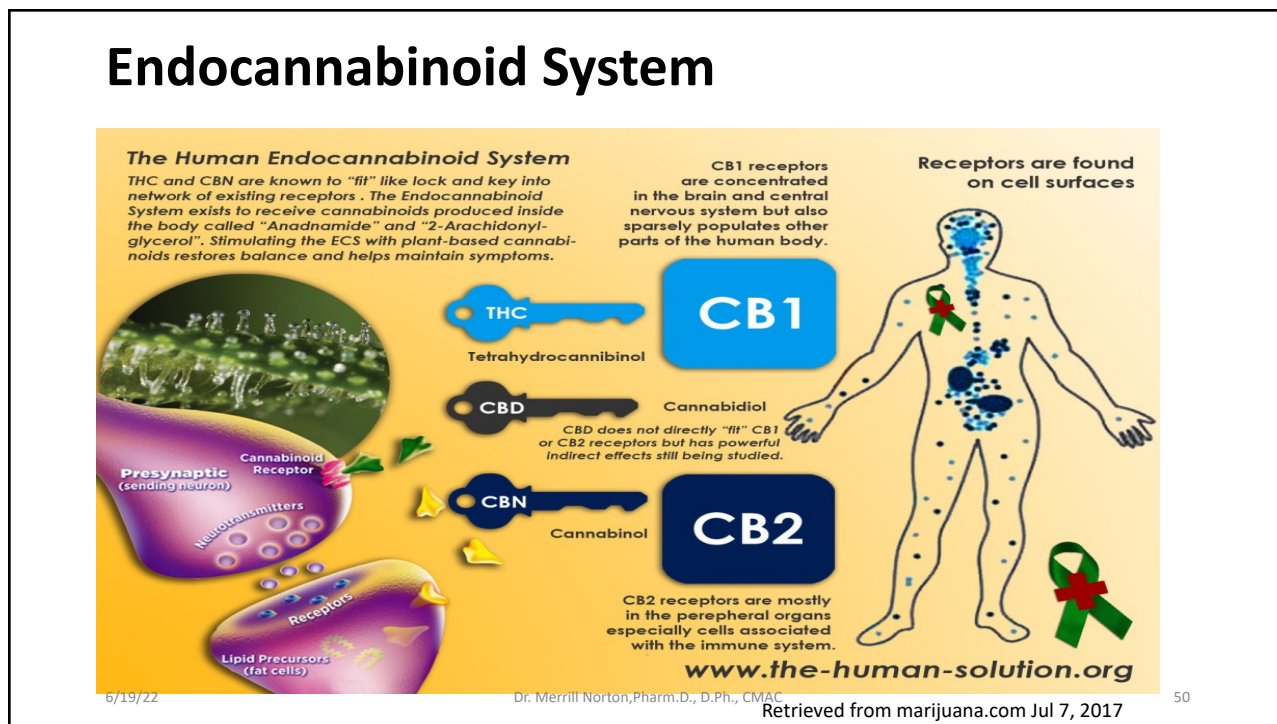
Rahn, B., 2014. Qualifying Conditions for Medical Marijuana by State, www.leafly.com

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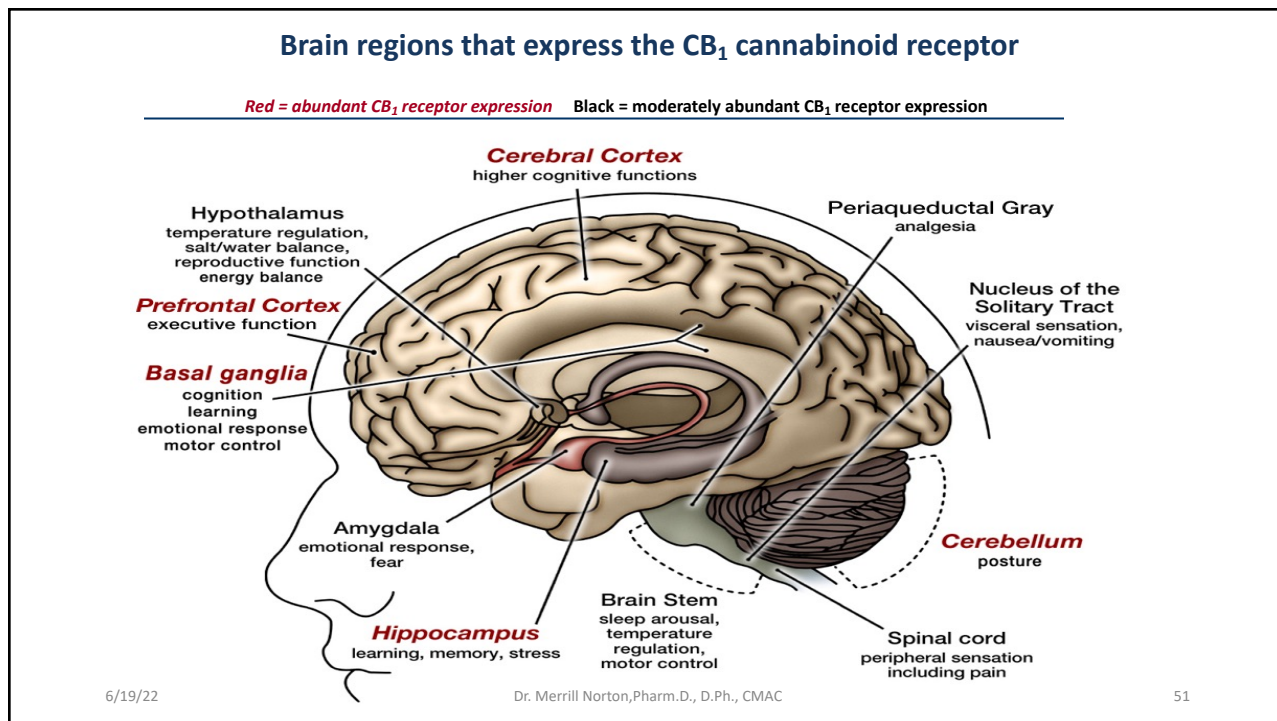
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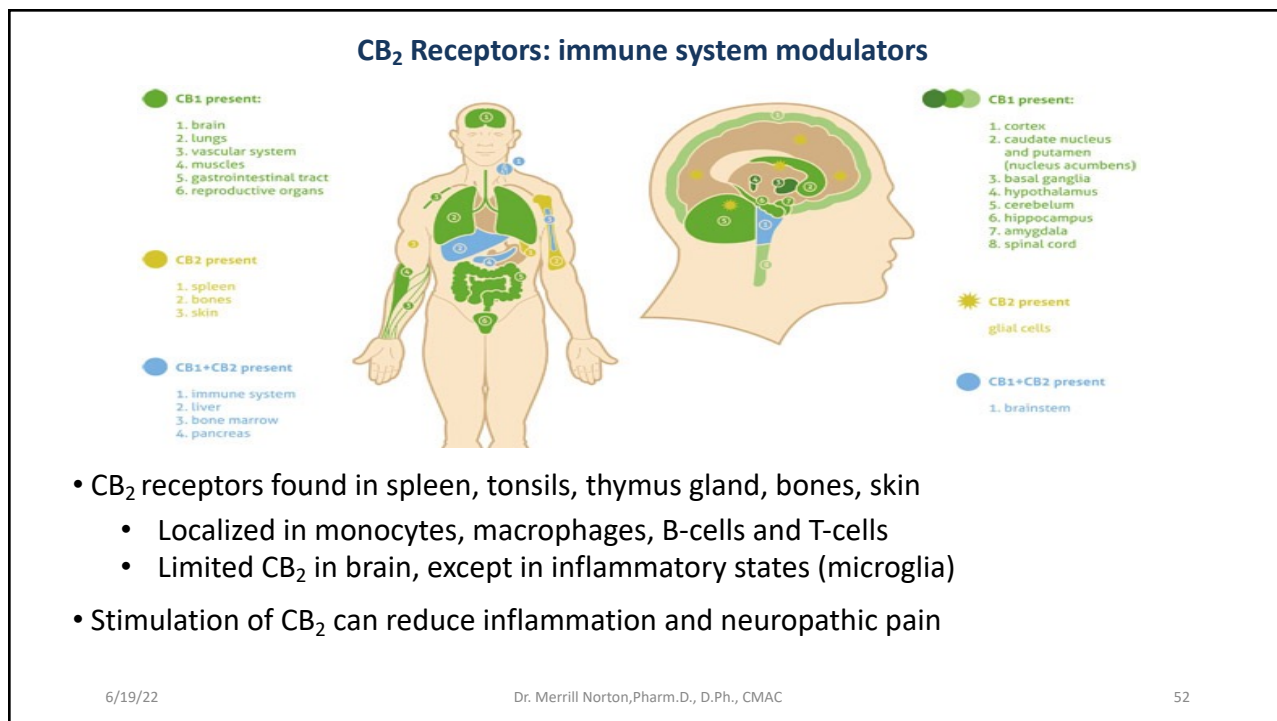
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50



51



52

T₁ H₄ C₃

C₃ B₃ D₂

T₁ H₄ C₃ V₄

C₃ B₃ N₁

C₃ B₃ D₂ V₄

C₃ B₃ C₃

>100 cannabinoids in the plant. Most are non-psychoactive.

Each has its own pharmacological actions and therapeutic potential.

The “Entourage Effect” may create both beneficial and detrimental effects of marijuana

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53

Phytocannabinoids

Marijuana vs Hemp

- Tetrahydrocannabinol (THC)
 - Psychoactive
 - Has medicinal value

- Cannabidiol (CBD)
 - Not Psychoactive
 - Has anxiety relieving properties
 - Antagonizes effects of THC
 - Has medicinal value

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54

Preclinical research identifies a range of possible therapeutic effects from phytocannabinoids

Cannabinoid	Intoxicates?	Possible Medicinal Application
THC	✓	<i>Nausea and Vomiting, Muscular Spasms, PTSD, Pain, Cancer, Inflammation,</i>
CBD	X	<i>Epilepsy, Psychosis, Anxiety, PTSD, Addiction, Dementia, Cancer, Insomnia</i>
CBDA	X	<i>Epilepsy, Nausea and Vomiting, Cancer</i>
CBDV	X	<i>Epilepsy</i>
THCA	X	<i>Nausea and Vomiting, Epilepsy</i>
THCV	X	<i>Diabetes, Obesity, Pain, Inflammation, Epilepsy</i>
THCVA	X	<i>Under investigation</i>
CBG	X	<i>Glaucoma, Cancer, Inflammation, Anxiety, Huntingdon's Disease</i>
CBGA	X	<i>Under investigation</i>
CBN	X	<i>Anxiety, Insomnia, Epilepsy, Anti-bacterial effects</i>
CBC	X	<i>Pain, Inflammation, Cancer</i>

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55

55

PubMed.gov

THC (Tetrahydrocannabinol)

- Psychoactive
- Analgesic
- Anti-inflammatory
- Antioxidant
- Anti-emetic
- Euphoric
- Anti-neoplastic
- Anti-spasmodic
- Anti-tremor
- Appetite Stimulant

CBD (Cannabidiol)

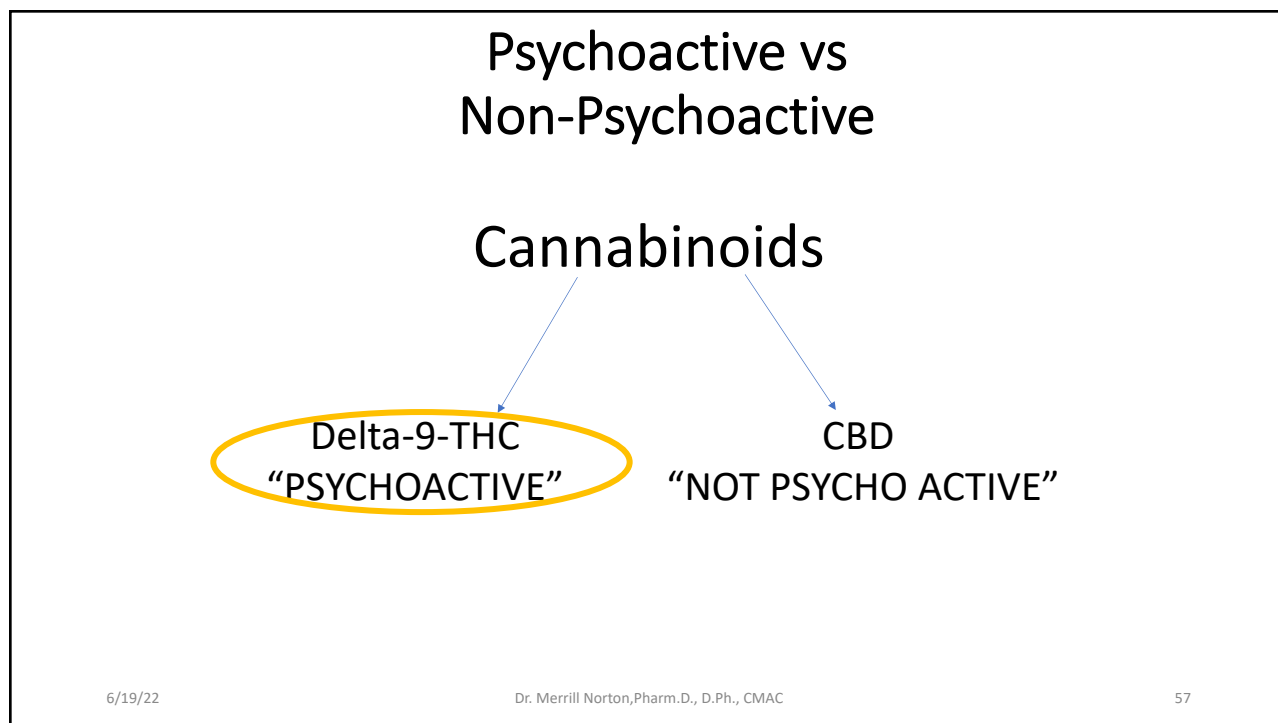
- Non-psychoactive
- Analgesic
- Anti-inflammatory
- Antioxidant
- Anti-emetic
- Anxiolytic
- Anti-psychotic
- Anti-convulsant/spasmodic
- Anti-epileptic
- Immunomodulatory
- Neuroprotective
- Decrease THC psychoactivity

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56

56



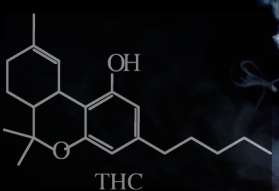
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Chemical Constituents of Cannabis


Chemical classes

- Cannabinoids (66)
- Nitrogenous compounds (27)
- Amino acids (18)
- Proteins/ enzymes (11)
- Sugars (34)
- Hydrocarbons (50)
- Simple alcohols (7)
- Simple aldehydes (12)
- Simple ketones (13)
- Simple acids (21)
- Fatty acids (22)
- Simple esters/lactones (13)
- Steroids (11)
- Terpenes (20)
- Non-cannabinoid phenols (25)
- Flavonoids (21)
- Vitamins (1)
- Pigments (2)
- Elements (9)

Total known compounds (483)



THC



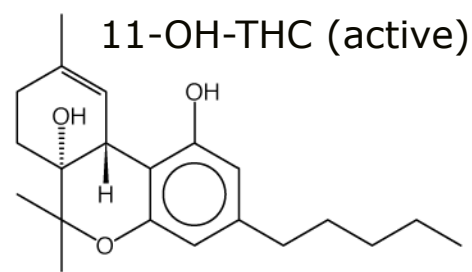
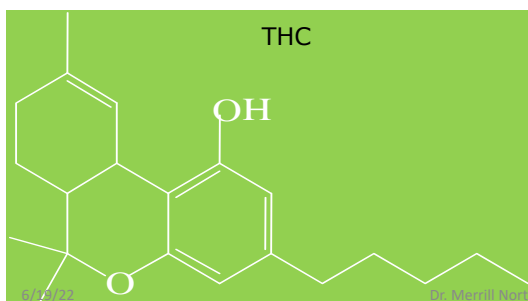
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58

✿ Delta-9-tetrahydrocannabinol (THC) is the active ingredient of marijuana

major metabolites OH-THC (11-delta-9-THC) and THC-COOH (11-nor-delta-9-THC-carboxylic acid, inactive)

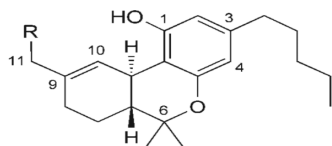
Levo is the more active isomer



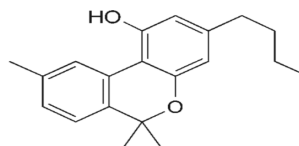
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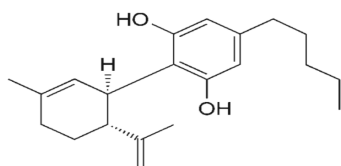
Cannabinoids



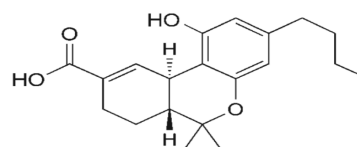
R = H Δ^9 -Tetrahydrocannabinol (THC)
R = OH 11-Hydroxy variant (11-OH-THC)



Cannabinol (CBN)



Cannabidiol (CBD)



'11-Nor-9-carboxy- Δ^9 -Tetrahydrocannabinol' (THC-COOH)

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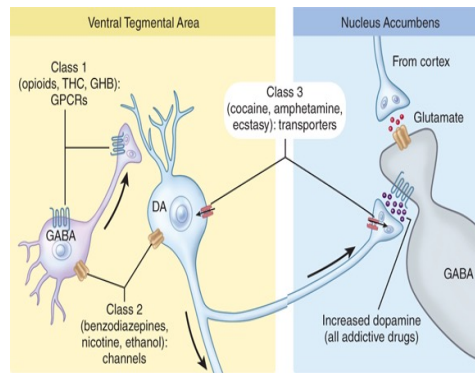
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Huestis, M. 2009, Human Cannabinoid Pharmacokinetics, *National Institute of Health: Chem Biodivers*, v. 4(8), p. 1770-1804.

60

60

THC: Pharmacodynamics Drug to Body



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology, 13th Ed.
www.accesspharmacy.com
Copyright © McGraw-Hill Education. All rights reserved.

- Causes disinhibition of dopamine (DA) neurons by presynaptic inhibition of GABA neurons in the VTA
- Causes euphoria and relaxation
- Feelings of well-being, grandiosity, and altered perception of passage of time
- Dose-dependent perceptual changes, drowsiness, diminished coordination, and memory impairment
- Hash (concentrated THC) may result in visual hallucinations, depersonalization, and frank psychotic episodes

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61

61

THC: Pharmacodynamics

a partial agonist at both CB1 & 2 receptors, has activity at non-CB receptors and other targets, and is responsible for the psychoactive effects of cannabis through its actions at the CB1 receptor.

smoking route or by vaporization: central nervous system and physiological effects occur within minutes

The psychotropic effect or "high" occurs much more quickly by the smoking than by the oral route

Physiological effects include rapid changes in heart rate and diastolic blood pressure, conjunctival suffusion, dry mouth and throat, vasodilatation, and decreased respiratory rate

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62

62

THC-Pharmacokinetics Body to Drug – Absorption

A. Inhalation/Smoking	90% of THC in blood circulates in plasma and rests in RBCs	Delta-9-THC is detectable in plasma within seconds after the first puff	Peak plasma concentration attained within 3 – 10 minutes
Bioavailability varies according to depth of inhalation, puff duration, and breath-hold	systemic bioavailability is ~23 – 27% for heavy users and 10 – 14% for occasional users	Maximum THC plasma concentration is observed 8 minutes after onset of smoking	Delta-9-THC plasma concentration rapidly decreases to 1 – 4ng/mL within 3 – 4 hours

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63

THC: Pharmacokinetics – Absorption

B. Oral Ingestion

relatively slower systemic absorption: 1 to 2 hours but can be delayed by a few hours

extensive liver metabolism reduces oral bioavailability of THC by 4 – 12%

maximum THC plasma concentration 4.4011ng/mL for 20mg and 2.7 – 6.3ng/mL for 15mg

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64



67

**To
Dab?**

**Or Not to
Dab?**



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68

68

Dabbing

- Inhalation of a concentrated tetrahydrocannabinol (THC) product created through butane extraction
- **Blasting**
 - pass butane through a steel or glass tube packed with dried cannabis trimmings
 - THC and other hydrophobic compounds in the plant's trichomes dissolve into the butane
 - butane-THC solution leaves the tube through filter and is collected in a dish or tray
 - butane evaporates and leaves resins that can have **THC concentration up to 80%**

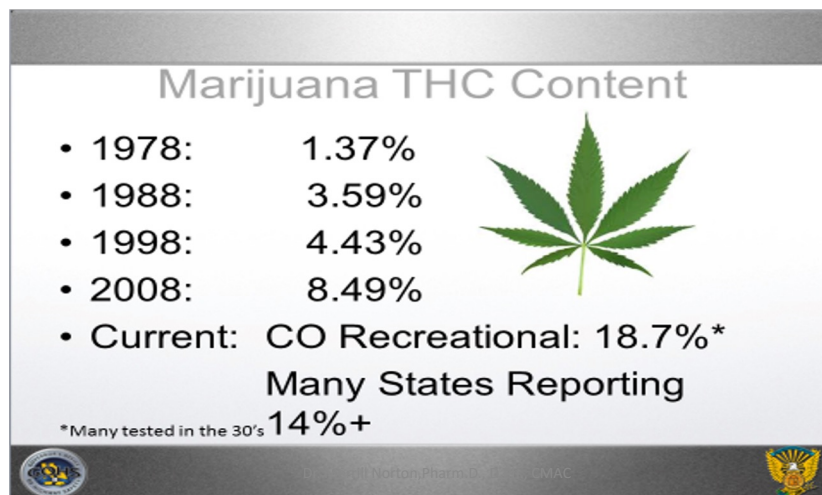
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69

69

Americans were getting high and addicted on marijuana with less than 5% THC in the 60s, 70s, 80s, and 90s.



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70

70


New Types of Concentrates


- Kief Up to 80% THC**
- Water Hash Up To 90% THC**
- CO2 Oil Up To 70% THC**
- Butane Hash Oil (BHO) 90%**
- Rosin Up To 80% THC**

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71

Vaping Extracts Like Ear Wax -
Up to 95% THC
Advertised in Magazines



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72

Vaping THC: A New Danger of Adolescents

- Adolescents who vape cannabis are at greater risk for respiratory symptoms indicative of lung injury than teens who smoke cigarettes or marijuana, or vape nicotine, a new University of Michigan study suggests.
- National probability sample (N = 14,798) of adolescents (12–17 years) using Population Assessment of Tobacco and Health Study data was used for this study.
- The odds of indicating “wheezing or whistling” in the chest were roughly two times higher among those who had used cannabis in ENDS (adjusted odds ratio 1.81, 95% confidence interval 1.47–2.22); neither e-cigarettes nor cigarettes had a significant association with all five respiratory symptoms in the fully adjusted models.
- Boyd, CJ et al, Cannabis, Vaping, and Respiratory Symptoms in a Probability Sample of U.S. Youth, **ADOLESCENT HEALTH BRIEF | VOLUME 69, ISSUE 1**, P149-152, JULY 01, 2021
DOI: <https://doi.org/10.1016/j.jadohealth.2021.01.019>

73

Vaping THC: A New Danger of Adolescents

- Female eggs exposed to THC, the psychoactive ingredient in marijuana, **have an impaired ability to produce viable embryos, and are significantly less likely to result in a viable pregnancy**, according to an animal study accepted for presentation at ENDO 2020, the Endocrine Society's annual meeting.
- 1. ElSohly et al., *Biol Psychiatry*. 2016 Apr 1;79(7):613-9.
- 2. El-Talatini et al., *PLoS ONE*. 2009 Feb 24;4(2):e4579.
- 3. Whan et al., *Fertil Steril*. 2006 Mar;85(3):653-60. 4. Wang et al., *Am J Physiol Endocrinol Metab*. 2012 Jun 15;302(12):1511-8.

74

MARIJUANA USE IS INCREASING IN PREGNANT FEMALES IN CALIFORNIA (2009-2016)

Figure 1. Adjusted Prevalence of Marijuana Use Among 279 457 Pregnant Females in KPNC by Screening Type, 2009-2016

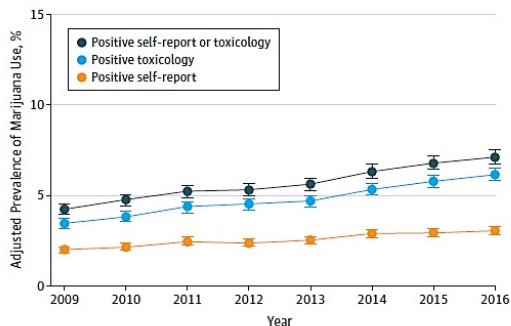
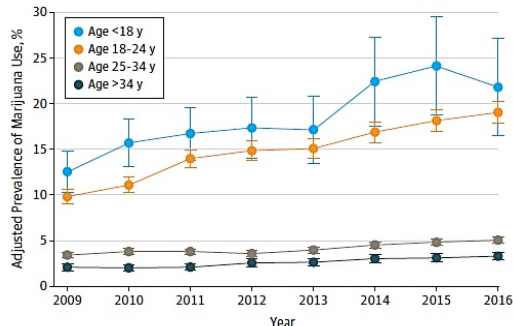


Figure 2. Adjusted Prevalence of Marijuana Use Among 279 457 Pregnant Females in KPNC by Age, 2009-2016

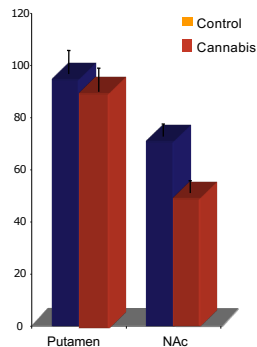
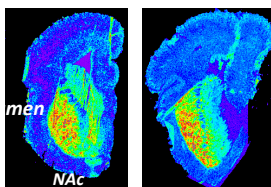


75

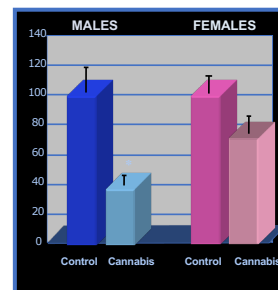
DOPAMINE D2 RECEPTOR BINDING IN THE STRIATUM AND AMYGDALA



Dopamine D2 receptor Striatum



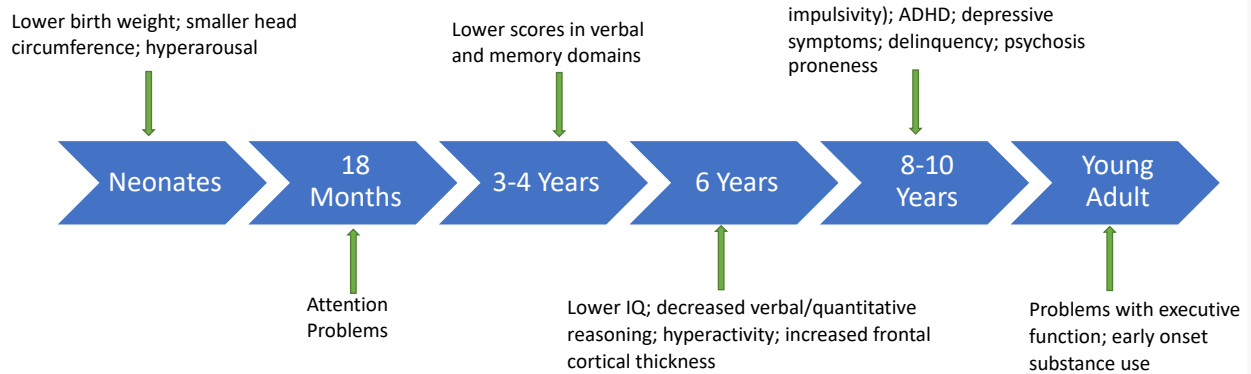
Amygdala



DiNieri et al Biol Psychiatry, 2011; Wang et al. Biological Psychiatry, 2004
Slide courtesy

76

PRENATAL CANNABIS EXPOSURE: OVERVIEW OF EFFECTS*



Adapted from W. Eric Kuhn, Intersection of Law, Policy, and Prevention, 2014; El Marroun, 2016, 2017 Fried PA et al, 1980, 1988, 1998, Day NL et al, 1991

* Multiple Caveats

77

Fertility Up In Smoke???

- **Science recognizes the impact of nicotine on fertility:**
- **Decreased egg quality and faster egg loss:** Nicotine, cyanide, and carbon monoxide, the chemicals in cigarette smoke, may speed up the loss of eggs and impair the quality of eggs and the function of your ovaries.
- **Earlier menopause:** Smoking can result in earlier menopause (one to four years before non-smokers).
- **Ectopic pregnancies:** Smoking cigarettes increases the risk of ectopic pregnancy (that's when the fertilized egg attaches in a place other than the uterus).
- **Sperm quality:** Smoking can adversely affect sperm motility (that's sperm's ability to move), sperm count, and morphology (that's the shape of sperm, and cigarette smoking may cause higher numbers of abnormally shaped sperm). Smoking can also decrease sperm's ability to fertilize eggs.
- <https://modernfertility.com/blog/vaping/>

78

THC and Fertility

High amounts of THC can decrease estrogen production and delay or impede ovulation. In a small study, 29 out of 201 women who smoked marijuana had delayed ovulation of between 1.7 to 3.5 days.

Some studies have found a link between marijuana use during pregnancy, which crosses the placenta, and increased chances of miscarriage, premature birth, and low birth weight.

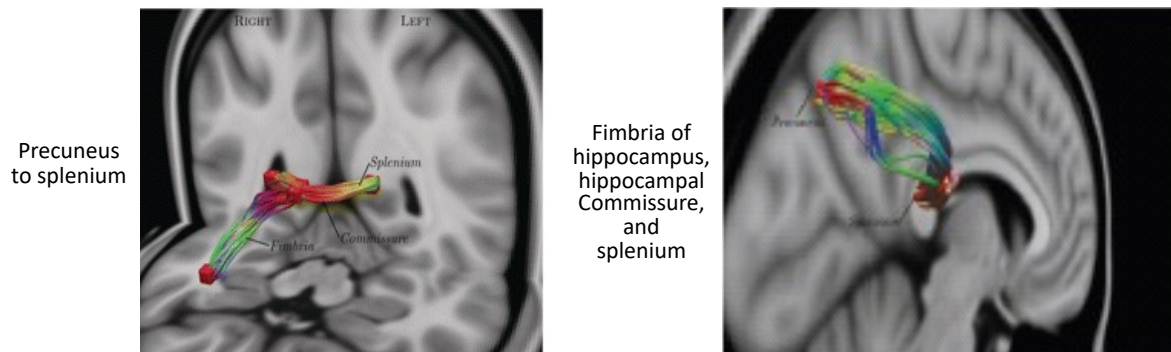
But like other aspects of research associated with marijuana, there have not been enough examinations separating variables so that medical professionals can ascertain what, if any, amount or form of cannabis pregnant women can use during gestation.

<https://www.havingbabies.com/blog-list/effects-of-marijuana-on-fertility-and-pregnancy/>

79

MULTIPLE STUDIES SHOW ALTERED BRAIN STRUCTURE AND FUNCTION IN YOUTH WHO REGULARLY USE CANNABIS

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



paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33).

: Zalesky et al Brain 2012

80

But Is THC Toxic???

- 2009 study from American Scientist on the relative toxicity of recreational drugs showed that using only 10 times the "effective" dose of alcohol could be fatal, whereas more than 1,000 times the effective dose of marijuana would have to be used to be possibly fatal.
- **The toxic dose of THC in a 65kg adult would be 8.45kg.**

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81

81

But is THC Toxic???

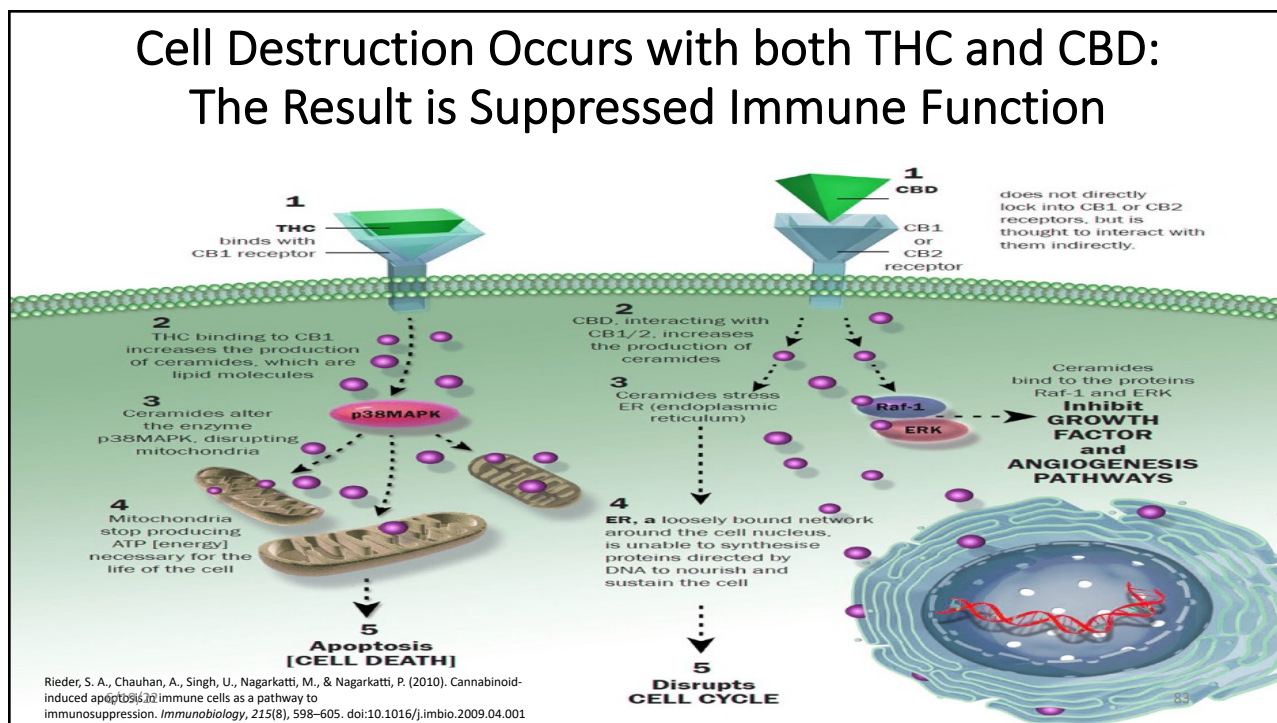
Yes

- The tachycardia almost invariably produced in acute intoxication, combined with the sensory alterations and increased tremor commonly reported, probably contribute to the affective components of these reactions.
- CNS and respiratory depression are noted with high doses, which in severe overdose may be life-threatening (Rosencrantz, 1983).
- These effects are, of course, more dangerous to those with pre-existing cardiac irregularities.
- Because of the large effective to lethal dose ratio in humans (probably in excess of 1:1000 in non-tolerant users) the risk of experiencing severe toxic effects of cannabis is limited by the aversive psychotropic effects of high doses, which usually lead to cessation of use before the onset of dangerous physical consequences.

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82

82



83

Impact of Addiction

■ MARIJUANA:

16 y.o.
2 year history of daily abuse

Normal

underside surface view of prefrontal and temporal lobe activity
© 2006 Amen Clinics Inc

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124

84

Symptoms of Cannabis Withdrawal

Withdrawal symptom	% (n) subjects reporting	Onset after quitting (days) (mean [SD])	Peak intensity (mean [median])
Craving for cannabis	59.4% (228)	4.4 (0.9)	4.4 (5.0)
Sleep difficulties	50.5% (194)	2.6 (4.9)	3.8 (4.0)
Insomnia	48.7% (187)	2.7 (5.0)	3.8 (4.0)
Feeling angry and/or aggressive and/or irritable	45.6% (175)	3.0 (5.5)	3.9 (4.0)
Feeling anxious, "nervous"	38.5% (148)	3.4 (6.5)	3.6 (3.0)
Change in appetite	36.4% (140)	3.7 (5.9)	3.9 (4.0)
Feeling sad, depressed	34.4% (132)	4.0 (6.7)	3.7 (4.0)
Feeling angry and/or aggressive	33.9% (130)	2.8 (5.4)	3.9 (4.0)
Feeling irritable, "jumpy"	29.4% (113)	3.3 (6.1)	3.7 (4.0)
Feeling angry	28.9% (111)	3.1 (5.7)	3.9 (4.0)
Physical symptom	25.3% (97)	3.1 (5.0)	3.6 (4.0)
Feeling restless	21.9% (84)	2.8 (4.4)	3.7 (4.0)
Feeling aggressive	20.1% (77)	3.6 (5.6)	3.8 (4.0)
Weight loss and/or decreased appetite	20.8% (80)	4.9 (8.1)	3.5 (4.0)
Increased appetite	20.8% (80)	3.3 (6.1)	4.0 (4.0)
Decreased appetite	17.4% (67)	4.0 (7.3)	3.6 (4.0)

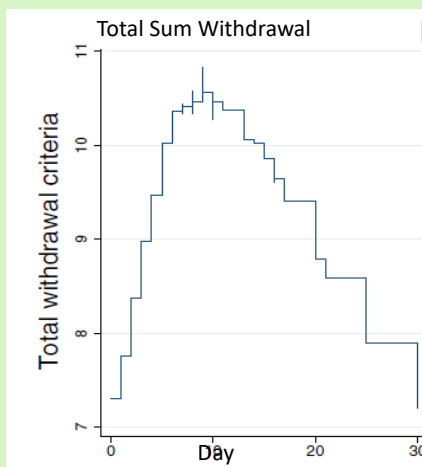
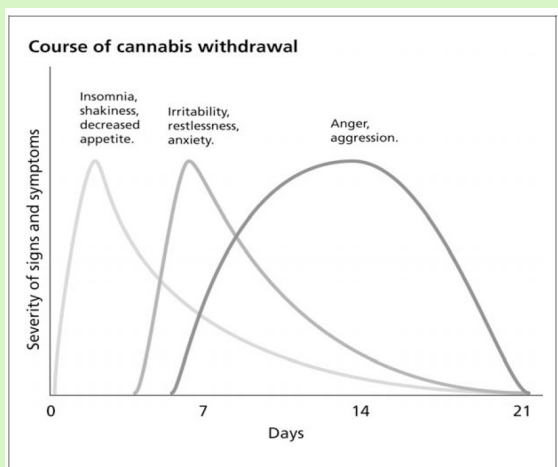
*Diagnostic criteria for cannabis withdrawal syndrome. Gorelick, D.A., et al (2012). Drug and alcohol dependence 123, 141-147.

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85

85

Withdrawal Time Course



NSW Drug and Alcohol Withdrawal Clinical Practice Guidelines. Mental Health and Drug & Alcohol Office, NSW Department of Health, Australia 2008
 Time-course of the DSM-5 cannabis withdrawal symptoms in poly-substance abusers Hesse and Thystrup BMC Psychiatry 2013, 13:258

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86

86

Cannabis

Drug Interactions of THC

Stimulants

- Cocaine, Amphetamines, etc
- increased hypertension
- tachycardia
- cardiotoxicity.

Depressants

- Benzodiazepines, Barbiturates, Ethanol, Opioids, Antihistamines, muscle relaxants, etc.
- increase drowsiness
- CNS depression

Alcohol

- greater impairment
- decreases in function
- less likely to react appropriately
- increased reaction times

National Highway Traffic Safety Administration, Cannabis / Marijuana (Δ 9 -Tetrahydrocannabinol, THC), 2012, Drugs and Human Performance Fact Sheets, <http://www.nhtsa.gov/people/injury/research/oh185drugs/cannabis.htm> (August 3, 2015)

87



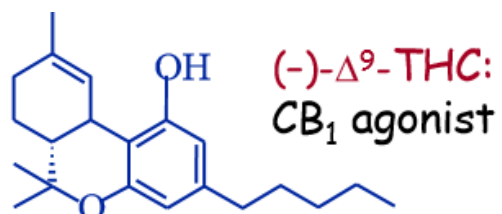
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88

88

THC - Structure



- **Converted from THCa by drying, heating.**

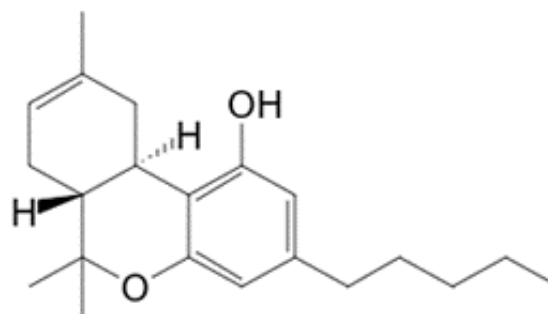
EpLink | The Epilepsy Research Program of the Ontario Brain Institute

91

91

Delta 8 THC

Delta 8 Cannabinoids



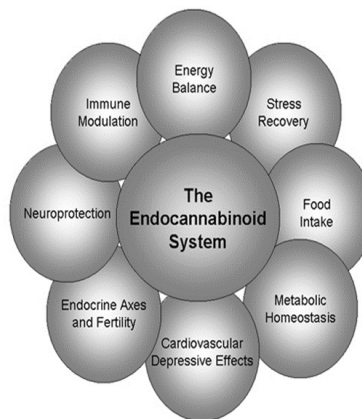
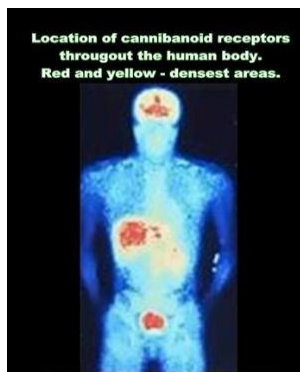
Dr. Martin Kerwin Pharm.D., D.Phil., FRCAC

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92

92

Made in the Brain: Endogenous Endocannabinoids



93



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94

94



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95

95



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96

96

What Is Delta 8 THC?

Unlike CBD, delta-8-THC produces euphoric effects that are similar to but milder than those of delta-9-THC, the well-known psychoactive compound in cannabis.

Delta-8-THC is an isomer of delta-9-THC. The only difference between the two molecules is the location of a double bond between two carbons.

The delta-8-THC craze began when an oversupply of CBD extracted from US-grown hemp caused the price of CBD to plummet.

Producers began looking for ways to turn the glut of CBD into something profitable. Using simple chemistry reported in the 1960s, the industry got creative and started experimenting with ways to convert CBD into delta-8-THC.

The resulting products target consumers who are looking to relieve stress and anxiety, especially those who don't want to use traditional cannabis products or those who live in places where cannabis products are not legally available.

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97

97

What Is Delta 8 THC?

But with no regulatory oversight and limited laboratory testing, most products sold as delta-8-THC are not actually pure delta-8-THC.

Such products typically contain a high percentage of delta-8-THC and small amounts of other cannabinoids, including delta-9-THC, and reaction by-products.

Some of the cannabinoids are not naturally found in cannabis. In most cases, nothing is known about the health effects of these impurities.

Several states are starting to crack down on sales of delta-8-THC products.

But as long as they are derived from hemp and contain no more than 0.3% of delta-9-THC on a dry-weight basis—the limit under federal law—many lawyers and hemp industry officials consider them legal.

Regardless of whether delta-8-THC is legal, chemists are sounding the alarm after finding several unidentified compounds in products labeled as delta-8-THC.

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98

98

Delta 8 THC and Pregnancy

- **How Cannabinoids Affect Obstetrical Outcomes:**
- Implantation, the attachment of the fertilized egg to the uterine wall, is dependent upon a number of tightly regulated processes. Evidence suggests that there are five ways in which cannabinoids can affect implantation:
- **Impairment of Fallopian Motility:** Cannabinoid signaling controls muscle contraction and relaxation in the fallopian tube responsible for the movement of a fertilized egg through the fallopian tube and into the uterus.
- **Ectopic Pregnancy:** [Previous studies](#) have shown that the blood collected from women who have had ectopic pregnancies contains significantly higher levels of the naturally occurring cannabinoid, anandamide, compared to normal pregnant controls. Consistency between human and animal data adds confidence that the observed findings in animal models of altered cannabinoid signaling may play a role in ectopic pregnancy.
- **Non-Hatched or Non-Viable Embryo:** In mice models known to have altered cannabinoid signaling, an increased mortality of offspring was observed in association with implantation of slowly developing embryos (6).
- **Decreased Uterine Receptivity:** It is theorized that the binding of exogenous cannabinoids to CB1 receptors in the uterus has embryotoxic effects on the uterine environment. Modeling of this scenario has halted the development of blastocysts *in vivo* and *in vitro* (7).
- **Miscarriage (Spontaneous Abortion):** Folic acid (Vitamin B9) is essential for embryo development and cannot be synthesized by the body which is why women are encouraged to take folic acid supplements during pregnancy. THC significantly decreases fetal folic acid uptake. Low levels of folic acid during pregnancy are associated with higher rates of miscarriages, as well as neural tube defects and low birth weight.

6/19/22

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99

99

Delta 8 THC and Pregnancy

- **How Cannabinoids Affect Embryo Development:**
- THC crosses the placenta, enters fetal blood circulation, passes through the blood brain barrier, and is found at the highest levels in fetal fat tissue. The brain is 60% fat and therefore stores THC following maternal ingestion. The brain is also densely populated with CB1 receptors which mediate THC's psychoactive properties.
- **Folic Acid Uptake:** As stated above, THC interferes with fetal folic acid uptake. Low levels of folic acid during pregnancy are known to be associated with neural tube defects and low birth weight.
- **Cellular Growth:** Exogenous cannabinoids may interfere with critical pathways for cellular growth and angiogenesis (formation of new blood vessels).
- **Neural Development:** Cannabinoids acting upon the CB1 receptor have the ability to influence the differentiation of neural cells from stem cells in the brain. This has tremendous potential to negatively affect learning and memory as well as developmental processes such as limb development.

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100

100

Delta 8 THC and Pregnancy

- **What are the effects of exposure to cannabis in the nursing infant?**
- The bioavailability of cannabis and its metabolites ingested by neonates in the breast milk has not been well-characterized. There are conflicting data regarding the outcomes of infants exposed to cannabis during breastfeeding and very few studies assessing outcomes in this population. These studies are not easy to conduct. First of all, recreational use of cannabis continues to be illegal in many states. Furthermore, it is difficult to disentangle the direct effects of cannabis delivered in the breast milk from the indirect effects of cannabis on the quality of childcare and parenting, especially in heavy, chronic users or when cannabis is combined with other substances.
- In one study, 136 breastfeeding infants were assessed at one year of age. In the 68 infants exposed to cannabis during the first month of life, there was evidence of decreased motor development at one year, when compared with matched infants who were not exposed to cannabis. Specifically, there was a 1465-point decrease in the Bayley index of infant motor development. However, the authors of this study cannot conclude that these findings were entirely due to exposure via breastfeeding, as many of the women also used marijuana during pregnancy.
- In another study, 27 breastfed infants exposed to cannabis were compared to 35 unexposed breastfed infants. At one year, no differences were noted for motor and mental development using the Bayley Scales of Infant Development. However, the small size of this study limited statistical analysis.
- So the jury is still out regarding the effects of cannabis on the nursing infant.
- Both the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics recommend that women refrain from using cannabis during pregnancy and while breastfeeding. Because of the persistence of cannabis and its byproducts in the breast milk for days to weeks, using cannabis and waiting for it to clear out of the breast milk is not a viable option. For women who use cannabis for medical indications, alternative therapies with more safety data during breastfeeding should be considered.

6/19/22

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101

101

Updated Marijuana Information Resources

- <https://themarijuanareport.org>
- <https://www.cdc.gov/marijuana/index.htm>
- <https://www.nccih.nih.gov/health/cannabis-marijuana-and-cannabinoids-what-you-need-to-know>
- <https://www.ncsl.org/bookstore/state-legislatures-magazine/marijuana-deep-dive.aspx>
- <https://www.health.harvard.edu/blog/medical-marijuana-2018011513085>
- <https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process>

102

CBD Product Testing

- <https://www.labcorp.com/assets/17241>
- <https://cptclabs.com/analytical-services/cbd-product-testing/>
- <https://www.badgerlabs.com/hemp-testing-packages-analysis/>
- <https://www.cbd-boxes.com/blog/guideline-for-cbd-product-testing-requirements/>
- <https://acslabcannabis.com/services/cbd-testing/>

103

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104

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105

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106

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107

Questions



108