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Disclosures

• No financial support from Pharmaceutical, Political, Commercial or Non Profit sources
• Member of NAMI
• Member of Minnesota Psychiatric Society
• Member of Minnesota Medical Society
• Member of Safe Approaches for Marijuana
• Wife is Board member of NAMI MN

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Cannabis: Neuro-Developmental, effects

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Cannabis has entered cultural parlance as a natural, safe, preferred, wellness product.

A NEW POLL HAS DETERMINED THAT BACON IS ONE OF THE HEALTHIEST FOODS YOU CAN EAT.
Cannabis through history

• Assyrians second millennium to 6\textsuperscript{th} century Used cannabis for psychoactive and medicinal purposes Their word was the drug that took away the mind.

• Moreau 1845 psychiatrist: gave concentrated oil of cannabis to experimental subjects. Conclusion: “there is not a single elementary manifestation of mental illness that cannot be found in the mental changes caused by Hashish”
Elucidation of the endocannabinoid system

- Cannabidiol structure elucidated in 1963
- 9 Delta tetrahydrocannabinoid synthesized in 1967
- CB1 receptor cloned in 1990 highest concentration in the brain. Found on GABAergic and Glutamatergic neurons
- CB2 receptor discovered in 1993 abundant in immune system
Cannabis use and mental disorders

PSYCHOSIS

• Regular use of cannabis associated with **Four times** increased risk of psychosis
• Relationship is **dose** dependent

Reference:
• Meta-analysis of the association between the level of cannabis use and risk of psychosis
Cannabis use and mental disorders

DEPRESSION

• Cannabis is also associated with increased risk for depression

Reference:

• The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies
  Psychological Medicine 2014: 44:797-810
Cannabis use and mental disorders

ANXIETY

- Increased odds of developing anxiety disorder

Reference:

- Cannabis use and prospective long-term association with anxiety: a systematic review and meta-analysis of longitudinal studies

Xue S, Husain MI et al:
Canadian Journal of Psychiatry
2021: 66: 126-38
Delta-9-Tetrahydrocannabinol
CBD Cannabidiol

Anti-oxidant anti-inflammatory anti-convulsant antagonist of THC
Both CBD and THC have a similar molecular structure: Differences in how the atoms are arranged accounts for the differing effects on the endocannabinoid system.

150 phytocannabinoids found in cannabis plant
NOVEL THC ISOMERS
Hexa hydro cannabinol
Tetra hydro cannabivarin
Tetra hydro cannabipherol THCP
• **THCP** delta 9 tetra hydro cannabiphorol

A phytocannabinoid Isolated from Cannabis sativa

In vivo affinity for CB1 receptor – **30 times higher than Delta 9 THC**

*Takeaway point:* The medicinal effects of cannabis based therapy is very variable possibly due to presence of differences in the product of extremely active phytocannabinoids such as THCP
High potency is how much?

- In Washington state’s legal market the gradient of potency spans
  - 20% for the flower to
  - 60% for concentrated extracts
Risks of High Potency Cannabis

PSYCHOSIS

• **High potency** cannabis was **three** times more likely to result in first episode psychosis

• **Low Potency** cannabis was not associated with psychosis compared to never use

Reference:

• Proportion of patients in South Lundon with First-episode psychosis attributable to use of high potency cannabis: A case control study
  Di Forti M, Marconi et al
  Lancet Psychiatry
  2015:2, 233-38.
Risks of High Potency Cannabis Substance use disorder

- **High potency** cannabis had **seven** fold increased risk of cannabis use disorder compared to **low potency** cannabis.

- Use of higher potency cannabis was associated with increased severity scores of CUD.

Reference:

- Examining the profile of high potency cannabis and its association with severity of cannabis dependence
  
  Freeman TP, Wostpcl AR
  Psychological Med 2015 45 3181-89
Risks of High Potency Cannabis Anxiety

• **High potency** cannabis was associated with **two times** risk of generalized anxiety disorder compared to low potency.

Reference

• Association of high-potency cannabis use with mental health and substance use in adolescence

Hines IA, Freeman IP, Gage SH et al
JAMA Psychiatry 2020; 77:1044-51
Risks of High Potency Cannabis

Anxiety

High, medium and low THC concentrations were correlated with feelings of anxiety.

Reference

Therapeutic satisfaction and subjective effects of different strains of pharmacological grade cannabis

Brunt TM, van Genugten M, et al

J Clinical Psychopharmacology 2014, 34: 344-49
Risks of High Potency Cannabis

DEPRESSION

- **No clear relationship** of high potency vs low potency for symptoms or diagnosis of depression.
- U.S. study of 191 subjects found no difference in the severity of depression of those using high or low potency cannabis.

Reference:
Endocannabinoid System

**Cannabinoid Receptor type 1**
Central and Peripheral NS
Liver, lung, GI Tract, urinary tract, thyroid, pancreas, heart, vascular endothelium, adipose tissue, reproductive organs, skeletal muscles

**Cannabinoid Receptor type 2**
Immune function
hemopoietic tissue
Somatostatins-secreting cells and Dopamine terminals striatum
HUMAN ENDOCANNABINOID SYSTEM

The most well-known cannabinoid receptors, CB1 and CB2, are proteins that are imbedded in the membrane of cells. These surface proteins are then attached to another protein that determines the signaling direction—activation or inhibition.

**CB1**
- CB1 Receptors target:
  - Appetite
  - Immune cells
  - Motor activity
  - Motor coordination
  - Pain perception
  - Short term memory
  - Thinking

CB1 Receptors are primarily found in the brain and central nervous system, and to a lesser extent in the other tissues.

**CB2**
- CB2 Receptors target:
  - Adipose tissue
  - Bone
  - Cardiovascular system
  - Central nervous system
  - Eyes
  - Gut
  - Immune system
  - Kidneys
  - Liver
  - Pancreas
  - Reproductive system
  - Respiratory tract
  - Skeletal muscle
  - Skin
  - Tumors

CB2 Receptors are mostly in the peripheral organs—especially cells associated with the immune system.
The Endocannabinoid (eCB) system plays a critical regulatory role in CNS structure and function throughout all developmental stages:

- cell fate (apoptosis)
- neuronal migration
- regulation of signaling pathways
- synaptic transmission in the mature central nervous system.
- glial formation
- axonal elongation
- fasciculation
- synaptogenesis
- synaptic pruning.
Endogenous cannabinoid Agonists

Arachidonoyl ethanolamine (AEA)
Affinity for CBR1

2 Arachidonoyl glycerol (2-AG)
Affinity for CBR1 and CBR2
Unusual neurotransmitters

• Actions are presynaptic – retrograde synaptic messenger not stored in vesicles
• Released post synaptically to activate presynaptic receptors.
Exogenous Agonist
Delta 9 Tetra hydro cannabinol partial agonist for both CB receptors feedback changing levels of: AEA and 2 AG
endogenous: muscarinic acetylcholine receptors > release of 2-AG > CB2R > suppresses D release
exogenous: D9THC > CB2R > suppress D release but dose dependent
The Cannabis neurodevelopmental question:
Can exposure to cannabis change the course of normal cellular processing and neurocircuitry leading to behavioral disturbances?
In utero exposure to THC:

NEUROTRANSMISSION-decreased expression of: dopamine D2 receptor
altered opioid receptor and opioid neuropeptide mRNA

NEUROANATOMY-
neurite branching
migration and differentiation of GABAergic and glutamatergic neurons

FUNCTIONAL-
working memory
ECb system regulates GABA

GABA signaling is critical for:
normal spontaneous network activity,
maturation and refinement of neuronal networks

Early THC exposure reduces:
• basal and stimulated GABA release in the hippocampus of adult rats
• increases the number of migrating GABAergic interneurons
• Delays GABA switching
Flipping the switch:

GABA is excitatory in the immature brain. GABA switching from excitatory to inhibitory transmission is a significant CNS regulatory maturation process. Delay in GABA maturation is associated with aberrant ultrasonic vocalizations, reflective of impaired early social communication and aversive affective state, in rat pups.
Fetal THC exposure: Effect at 10 years of age

In a cross-sectional study of 11,875 children mean age 9.8 years controlling for family history of mental illness, maternal age, family income, ethnicity, two groups were identified

Group one: maternal exposure after knowledge of their pregnancy;
Group two: maternal exposure only before maternal knowledge of pregnancy

Group one child outcomes compared to Group two child outcomes showed more....

**Psychotic Like Experiences:** corrected $P$ value .02
**Internalizing disorders:** corrected $P$ value .05
**Externalizing Disorders:** corrected $P$ value <.001
**Attention problems:** corrected $P$ value <.001
**Thought disorder:** corrected $P$ value <.001
**Social problems:** $P$ value <.001

source: *JAMA*, 2020
Lactation delivered Neonatal Effects of THC

- electrophysiological disturbances that persist into adulthood
- hypo excitability of pyramidal neurons (layers 5 and 6) associated with impairment of synaptic plasticity in the PreFrontal Cortex
- total abolishment of NMDA-mediated LTP and LTD. LTP is responsible for the increase in the efficiency of synaptic conduction.
- NMDA N-methyl-D-aspartate receptor is a glutamate receptor
Lactation delivered Neonatal Effects of THC

- eCB-mediated Long Term Depression has diverse roles in learning and memory.
- LTD involved in pathological states: drug addiction, mental retardation and neurodegenerative diseases such as Alzheimer's disease.
Summary of eCB effect on GABA

Human studies of children who were exposed to THC during lactation is lacking, however animal models are instructive. These preclinical studies suggest an impact on neural network assembly, disturbance of the physiological trajectory of major neurotransmitter systems, dysregulation of the balance between excitation–inhibition leading to dysfunction in synaptic plasticity and behavioral disruptions through to adulthood.
Cannabis exposure during early childhood:

• Children exposed to second hand cannabis smoke show THC levels in all body fluids.

• Higher maternal cannabis use across the infant toddler period was predictive of higher behavior problems at 2 years.
Cannabis exposure during adolescence:

• The eCB system mediates adolescent maturation related neural reorganization

Delayed maturation due to THC: altered gliogenesis in the striatum, increased oligodendroglia relative to controls. A single dose of THC transiently abolished eCB mediated Long term depression (LTD) in the nucleus accumbens and hippocampus of adolescent mice.

• Gray Matter Volume difference associated with low levels of cannabis use in adolescence: Greater gray matter volume in hippocampus, amygdala, striatum and parietal regions

• Symptoms of agoraphobia and sensation seeking

Cannabis exposure during adulthood: Acute and chronic effects and differences based on dose. Receptors in different parts of the body are stimulated differently and therefore THC effects are dose dependent. Low dose may produce euphoric/wellbeing and higher doses may cause cognitive and mental health disorders.

American Journal of Psychiatry Volume 179, March 2022
Mar 2022
July 1 2022 Cannabis Edible/ Drinkable Law: Manufacturers’ requirements:

- All products to be tested
- Labels must contain Name, address and phone of manufacturer and testing lab
- Accurate statement of amount of cannabinoids
- Statement that the product does not claim to diagnose, treat, cure, or prevent any disease and has not been evaluated or approved by the FDA
- Packaging and product must not bear the likeness or contain cartoon-like characteristics that appeals to children;
- Be packaged in a way that resembles the trademarked, characteristic, or product-specialized packaging of any commercially available food product.
- Not to be infused with an alcohol beverage
# Edibles dosing chart

<table>
<thead>
<tr>
<th>THC per dose</th>
<th>What to expect</th>
<th>Who’s it for?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 - 2.5 mg</strong></td>
<td>Mild relief of pain, stress, anxiety, and other symptoms&lt;br&gt;Improved focus and creativity</td>
<td>First-time consumers&lt;br&gt;Microdosing</td>
</tr>
<tr>
<td><strong>5 mg</strong></td>
<td>Stronger symptom relief&lt;br&gt;Euphoria&lt;br&gt;May impair coordination and alter perception</td>
<td>Recreational consumers&lt;br&gt;Patients with persistent symptoms&lt;br&gt;Restless sleepers</td>
</tr>
<tr>
<td><strong>10 mg</strong></td>
<td>Strong euphoria&lt;br&gt;May impair coordination and alter perception&lt;br&gt;New consumers may experience negative effects</td>
<td>High tolerance THC consumers (both recreational and medical)</td>
</tr>
<tr>
<td><strong>20 mg</strong></td>
<td>Very strong euphoria&lt;br&gt;Likely to impair coordination and alter perception</td>
<td>Consumers with significant THC tolerances&lt;br&gt;Patients with a decreased GI absorption</td>
</tr>
<tr>
<td><strong>50 – 100 mg</strong></td>
<td>Seriously impaired coordination and perception&lt;br&gt;Can cause unpleasant side effects including nausea, pain, and rapid heart rate</td>
<td>Experienced, high-tolerance THC consumers&lt;br&gt;Patients living with cancer, inflammatory disorders, or conditions that necessitate high doses</td>
</tr>
</tbody>
</table>

Please note that everybody processes cannabis differently and could have a different edibles experience. Always start low and slow and follow packaging guidance. Visit Leafly.com for more resources.
Proposed guardrails for new cannabis edibles/drinkables

1. Include a warning on the label declaring THC to be hazardous to a user’s mental health.

2. Controls on site of purchase to allow adequate testing for potency and isomers due to limitations in lab capacity.

3. Limit time of day for purchase of edibles and drinkable with an understanding of THC’s extended intoxicant effect.

4. A broad well-funded education program to help citizens understand the different effects of Cannabidiol, delta-8 THC, delta-9 THC, delta-10 THC, and other isomers.
Proposed guardrails for new cannabis edibles/drinkables

- 5. A specific preventive educational program that informs of the harms to the fetus, infants and school age children from second hand smoke and diversion of products to adolescents.
- 6. Limitations on the quantity of purchase to prevent binge use and diversion to non-purchasers.
- 7. Taxation of the product to recoup the costs to the state and counties of addiction, vehicular accidents, family problems and child placement due to neglect and abuse.
Proposed guardrails for new cannabis edibles/drinkables

8. Impanel a task force to compile data related to societal changes from cannabis-related harms including: high school suspensions, psychosis, depression and anxiety disorders, cannabis impaired drivers, the proliferation of THC isomers at retail establishments.

9. A cost benefit analysis of the sum of taxes raised from THC sale and the sum of loses from the mental health/substance use, traffic accidents and loss of function to students and employers and employees.

10. And most importantly an assessment of the differences in harms among the BIPOC population.