

CANNABIS: SCIENCE-INFORMED POLICIES



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Disclosure

- No financial disclosure
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Cannabis: The "Wonder Drug"

RISKS

BENEFITS



Cannabis — Changing Sociopolitical Landscape

ÅSAM

I-weed YOU-weed HE-weed SHE-weed IT-weed

YOU-weed THEY-veed

WE-WEPA

Wide availability Reduced risk perception Increased THC concentration Cheaper cost for young people Distrust of government Social media

Vulnerable developing brain

THE PERFECT STORM



ENDOGENOUS CANNABINOID SYSTEM IS CRITICAL FOR HARDWIRING OF THE BRAIN

- The endocannabioid system is involved in a wide range of developmental processes
- CB1R mRNA expressed in the human fetal brain

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- Cannabinoid receptors preferentially localized to axonal tracts and growth cones and regulate neurite development
- In Utero cannabis exposure associated with changes in the expression in the brain of multiple genes including SCG10 (stathmin-2; cytoskeletal organization) and Dopamine D2 receptors (implicated in addiction and psychiatric disorders)







SCG10: Cytoskeletal gene

DOPAMINE D2 Receptor

Tortoriello et al. EMBO J. 2014 Apr 1;33(7):668-85



Prenatal THC Exposure Alters Sensitivity to other drugs (e.g., Heroin) in Adulthood

PRENATAL CANNABIS EXPOSURE LEADS TO PROTRACTED DISRUPTIONS IN ADULTHOOD OF BEHAVIOR, NEURONAL MORPHOLOGY, PHYSIOLOGY AND GENE EXPRESSION RELATED TO SYNAPTIC PLASTICITY







Spano et al, Biological Psychiatry, 61:554-63, 2007

PRENATAL CANNABIS EXPOSURE LEADS TO PROTRACTED DISRUPTIONS IN ADULTHOOD OF BEHAVIOR, NEURONAL MORPHOLOGY, PHYSIOLOGY AND GENE **EXPRESSION RELATED TO SYNAPTIC PLASTICITY**

> vehicle THC

Drug intake - mild stress





Synapse-related genes



Spano et al, Biological Psychiatry, 61:554-63, 2007

Tortoriello et al. EMBO J. 2014 Apr 1;33(7):668-85





Stress (and Cannabis) in Pregnancy Project Superstorm Sandy - 2012

Yoko Nomura





"Double Hit" Consequences of Prenatal Cannabis and Stress

- Increased glucocorticoid (stress hormone) receptor and decreased placenta cannabinoid receptor gene expression
- Increased Anxiety and aggression at 4 years of age
- Increased stress hormone levels (cortisol and DHEA) and glucocorticoid receptor gene expression

Effects of Cannabis Exposure During Development: Human Longitudinal Studies



Fried et al., Neurotoxicol Teratol 25(4):427-436 Goldschmidt et al., 2004, 2008; Day et al, 2006

18-22 yrs: increased neural

LONG TERM EFFECTS OF ADOLESCENT CANNABIS USE

Cannabis consumption at age 18 and later risk of schizophrenia



Adjusted odd ratios of different outcomes, by frequency of teen marijuana use



Source: "Young adult sequelae of adolescent cannabis use: an integrative analysis"



Long term Effects of Adolescent Cannabis Use

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Greater levels of cannabis consumption at age 18 correlated with later risk of schizophrenia



Daily adolescent use associated with:

- 18 times more likely to become dependent on cannabis
- 8 times more likely to use other illegal drugs in the future
- 7 times more likely to attempt suicide

Long term Effects of Adolescent Cannabis Use

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- Increases heroin selfadministration in adulthood
- Reduces the normal development of neuronal branching (communication) in the prefrontal cortex
- Alters the structural development of the prefrontal cortex along with associated perturbations in gene expression networks relevant to psychiatric risk

LONG TERM EFFECTS OF ADOLESCENT CANNABIS USE

Neuronal Morphology



Gene Expression







Cannabis



PHYTOCANNABINOIDS

Cannabis contains over 500 chemicals including >140 cannabinoids which have a greater or lesser degree of psycho-pharmaco-activity

- Tetrahydrocannabinol (THC)
- Cannabidiol (CBD)
- Tetrahydrocannabinolic Acid (THCA)
- Cannabinol (CBN)
- Cannabigerol (CBG)
- Cannabichromene (CBC)
- Tetrahydrocannabivarin (THCV)
- Cannabidivarin (CBDV)

THC AND CBD: CANNABINOIDS WITH DIFFERENT ACTIONS







THC AND CBD: CANNABINOIDS WITH DIFFERENT ACTIONS - PSYCHOSIS

Tetrahydrocannabinol (THC)

- Acute administration of THC Increases:
 - total symptom severity
 - positive symptom severity
 - negative symptom severity
- Daily cannabis use and use of high-potency cannabis contributes to higher incidence of psychotic disorder

Di Forti et al.,Lancet Psychiatry, 6(5):427-436, 2019 Hindley et al, Lancet Psychiatry 7(4):344-353, 2020 McGuire et al., Am J Psychiatry, 175: 225–231, 2018



THC AND CBD: CANNABINOIDS WITH DIFFERENT ACTIONS

- PSYCHOSIS

Cannabidiol (CBD)

- CBD attenuates the pro-psychotic, anxiety and cognitive effects elicited by THC in healthy individuals.
- CBD reduces positive symptoms in schizophrenia patients
- CBD appear effective in patients at clinical high risk and those with first episode psychosis
- Weak evidence for improvement of cognition
- Inverted-U dose-response curve for some effects

Di Forti et al.,Lancet Psychiatry, 6(5):427-436, 2019 Hindley et al, Lancet Psychiatry 7(4):344-353, 2020 McGuire et al., Am J Psychiatry, 175: 225–231, 2018 THC and CBD show opposite effects on regional brain activation across a variety of cognitive tasks in healthy individuals

CAN CBD MODULATE DRUG DEPENDENCE?





DISTINCT EFFECTS OF THC AND CBD ON HEROIN VULNERABILITY – ANIMAL MODEL







Human Study: Double-Blinded Placebo Control CBD Study For Opioid Use Disorder

CUE-INDUCED EFFECTS: <u>CRAVING</u> visual analog scale (vas)-c





Hurd et al., Am J Psychiatry, 2019



Human Study: Double-Blinded Placebo Control CBD Study For Opioid Use Disorder

CUE-INDUCED EFFECTS: <u>ANXIETY</u> VISUAL ANALOG SCALE (VAS)-A







Hurd et al., Am J Psychiatry, 2019

CBD MAY HOLD PROMISE FOR:

- Addiction (craving and anxiety)
- Psychosis, Anxiety
- Insomnia (high dose sedative effects)

CBD UNSURE REGARDING:

- Pain (inflammation)
- Autism and other developmental disorders
- Neurological disorders

Medical Cannabidiol?





Medical Cannabidiol?

Dose, treatment regimen, etc need to be fully determined

Formulations/delivery systems need to be developed

Urgency for clinical trials

RISKS

SUD

Psychosis

Anxiety/negative affect

Negative impact on the developing brain

BENEFITS

SUD (opioid; tobacco, cannabis, alcohol)
Psychosis
Anxiety/negative affect
Developmental disorders
Pain/inflammation
Epilepsy



RISKS

SUD (THC)

Psychosis (THC)

Anxiety/negative affect (THC)

Negative impact on the developing brain (THC)

BENEFITS

SUD (opioid; tobacco, cannabis, alcohol) (CBD)
Psychosis (CBD)
Anxiety/negative affect (CBD)
Developmental disorders (CBD?; THC?)
Pain/inflammation (CBD?; THC)
Epilepsy (CBD)



MANY OUTCOMES ARE STILL UNCERTAIN ABOUT BOTH THC AND CBD



MOVING FORWARD FOR SCIENCE-INFORMED POLICY



final syllable of derivation). ter·mi·nol·ogy /,ta (science of the) pr in a science or orammatical



EDUCATION TO INFORM AND CHANGE "RISK PERCEPTION"

TERMINOLOGY MATTERS

INCLUSION OF SCIENCE IN POLICY

