



Contemporary Priorities in Cannabis Research: A Translational Approach

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Disclosures

James MacKillop, PhD

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No intellectual conflicts of interest

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Overview

- DeGroote Centre for Medicinal Cannabis Research
- A translational approach to cannabis research
- The gamut of research possibilities across the translational spectrum
- Conclusions

Acknowledgements



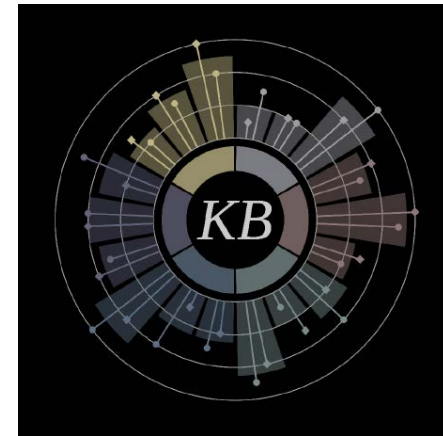
Amanda Doggett, PhD



Andre McDonald, PhD



Aysha Cooper, MSc



Kyla Belisario, MA



Michael G. DeGroote

CENTRE FOR MEDICINAL CANNABIS RESEARCH

www.cannabisresearch.mcmaster.ca

Vision and Mission

Vision

An evidence-based understanding of medicinal cannabis, encompassing both its potential therapeutic effects and associated risks.

Mission

To leverage the highest standards of research methodology to advance the understanding of medicinal cannabis.

Strategy:

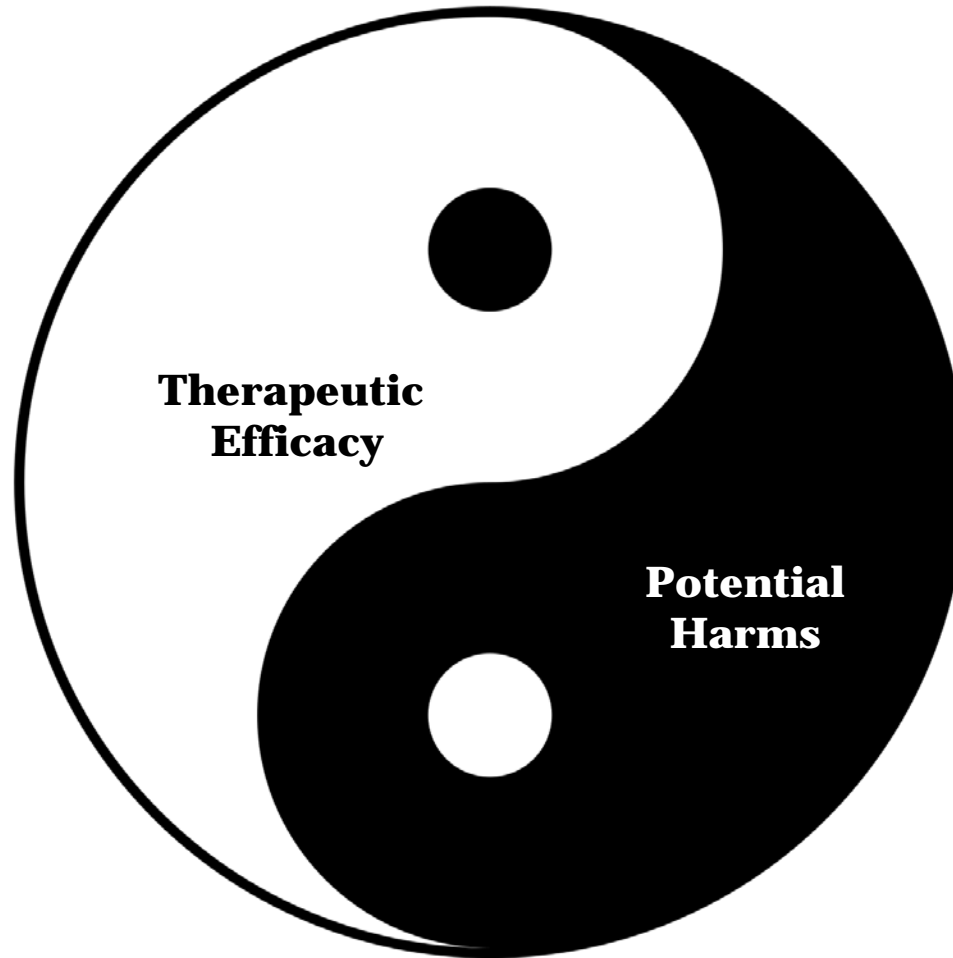
- ❑ Create a network of researchers and clinicians dedicated to an evidence-based understanding of cannabis
- ❑ Conduct innovative research projects to advance scientific discovery
- ❑ Curate the scientific body of knowledge on cannabis

Creating a Network



Priority Areas

***On-target
Benefits***



***Off-target
Harms***

Priority Areas

Therapeutic Benefits

- Pain
- Sleep disorders
- Substance use disorders
- Anti-microbial resistance

Adverse Consequences

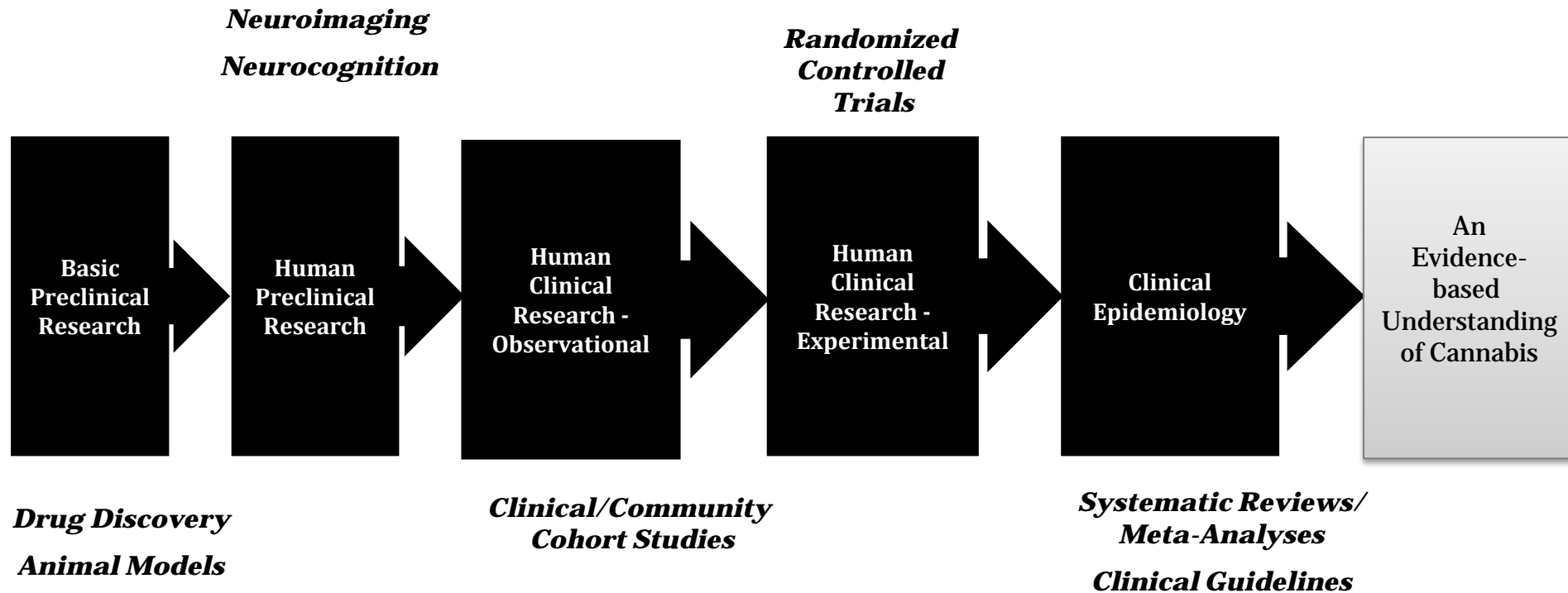
- Cannabis use disorder
- Psychiatric disorders
- Neurocognitive effects
- Lung harms
- Pregnancy-related harms

Impact of Legalization

Translational Framework

An Evidence-based Understanding of Cannabis

Translational Framework



Cannabis Research Across the Translational Spectrum

Cannabis Constituents

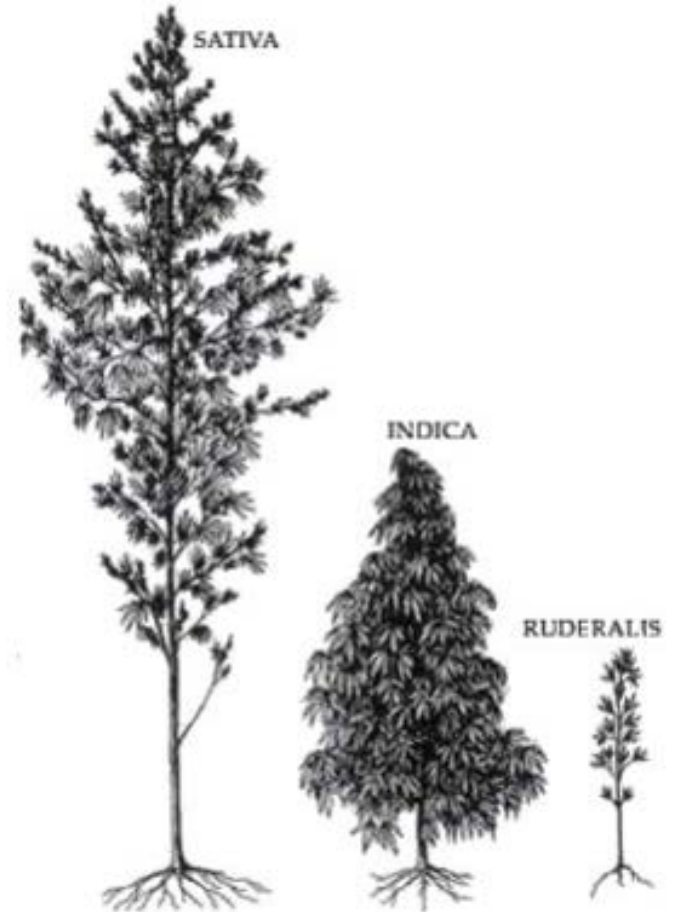
Sativa



Indica

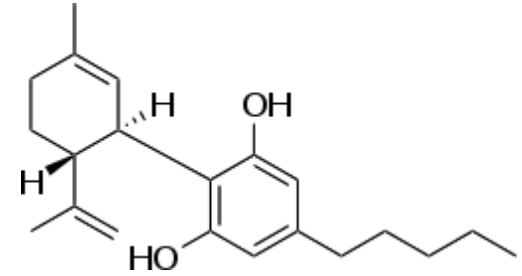
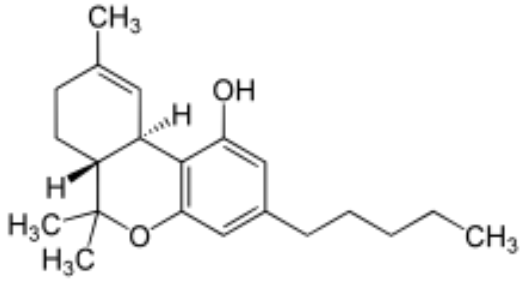


*“There are biochemically distinct strains of Cannabis, but the sativa/indica distinction as commonly applied in the lay literature is **total nonsense** and an **exercise in futility.**”*



Piomelli & Russo (2016) *Cannabis & Cannabinoid Research*

Cannabis Constituents



Δ^9 -Tetrahydrocannabinol (THC)

Cannabidiol (CBD)

Cannabinol (CBN)

Cannabigerol (CBG)

Cannabichromene (CBC)

>500 constituents

>100 cannabinoids

Camphene

Terpineol

Δ -3-carene

Limonene

Eucalyptol

Humulene

Trans-neroliol

Myrcene

Linalool

α Bisalol

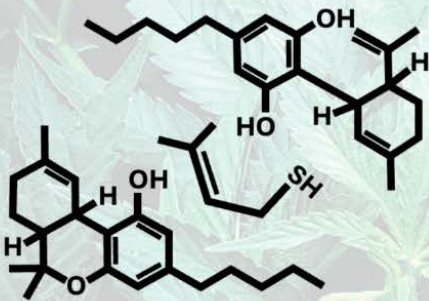
Borneol

Caryophyllene

α Pinene

β Pinene

Cannabis Constituents



Browse Cannabis Compounds >>

Learn More >>

<https://cannabisdatabase.ca/>

Cannabis Constituents

Browsing Compounds

Filter by physiological effects :

- Allergen
- Analgesic
- Anxiolytic
- Carcinogen
- Disinfectant
- Flavoring agent
- Goitrogen
- Immunosuppressant
- Insect attractant
- Insect repellent
- Insecticide
- Irritant
- Larvacide
- Mood changes
- Neuroprotective
- Obesogen
- Perfuming agent
- Plant hormone
- Psychoactive
- Sedative
- Stimulant
- Toxin
- Uremic toxin
- Pro-oxidant
- Oxidizing agent

Filter by physiological counter-effects :

- Anti-acetylcholinesterase
- Anti-bacterial
- Anti-cancer
- Anti-convulsant
- Anti-depressive
- Anti-diabetic
- Anti-inflammatory
- Anti-nociceptive
- Anti-oxidant
- Anti-parasitic
- Anti-viral
- Anti-microbial
- Anti-fungal
- Herbicide
- Pesticide

Filter by compound categories :

- Primary Metabolites
- Secondary Metabolites
- Smoke Condensate Compounds
- Lipids
- Cannabinoids
- Polyphenols
- Fatty acids
- Terpenoids
- Esters
- Alkanes
- Phytoestrogens
- Herbicides/fungicides

Filter by compound status :

- Detected and quantified
- Detected but not quantified
- Expected but not quantified

Clear

Apply Filter

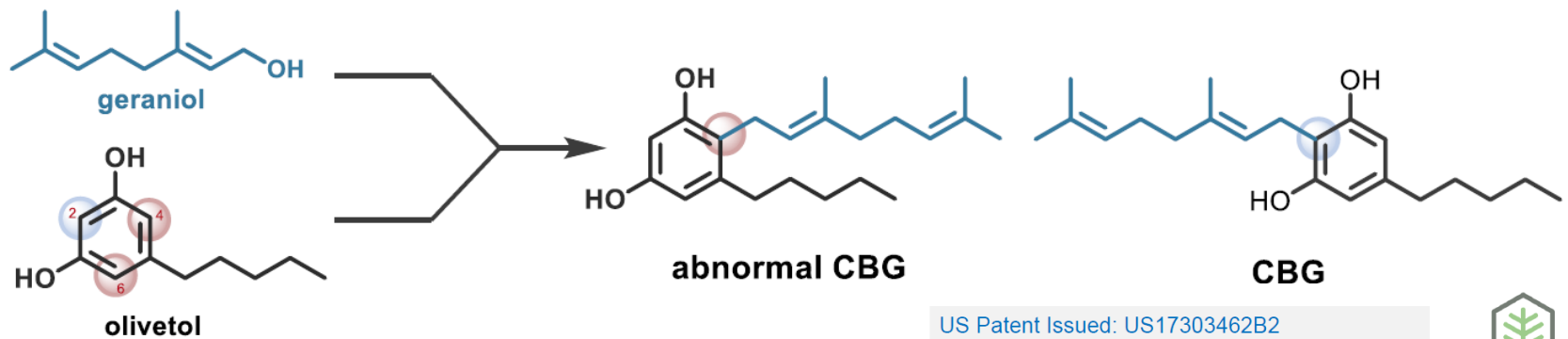
Displaying compounds 1 - 25 of 6258 in total

<https://cannabisdatabase.ca/>

Synthesis of Cannabis Constituents



Dr. Jake Magolan

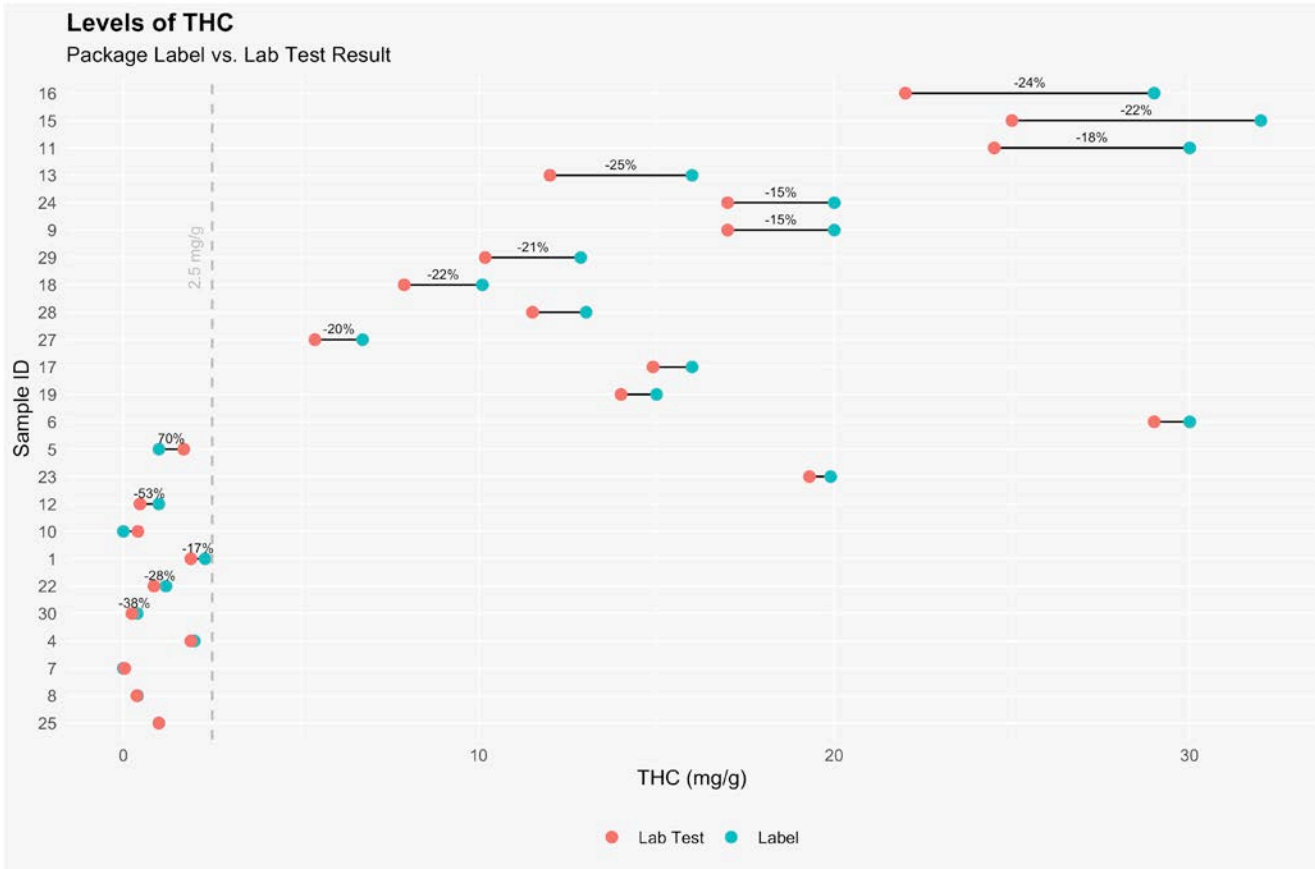


US Patent Issued: US17303462B2
Canadian Patent Pending: CA3081858A1
European Patents Pending: WO2021237371A1



https://www.youtube.com/watch?v=rJ_v5-w5GME&t=1340s

Cannabis Product Constituents

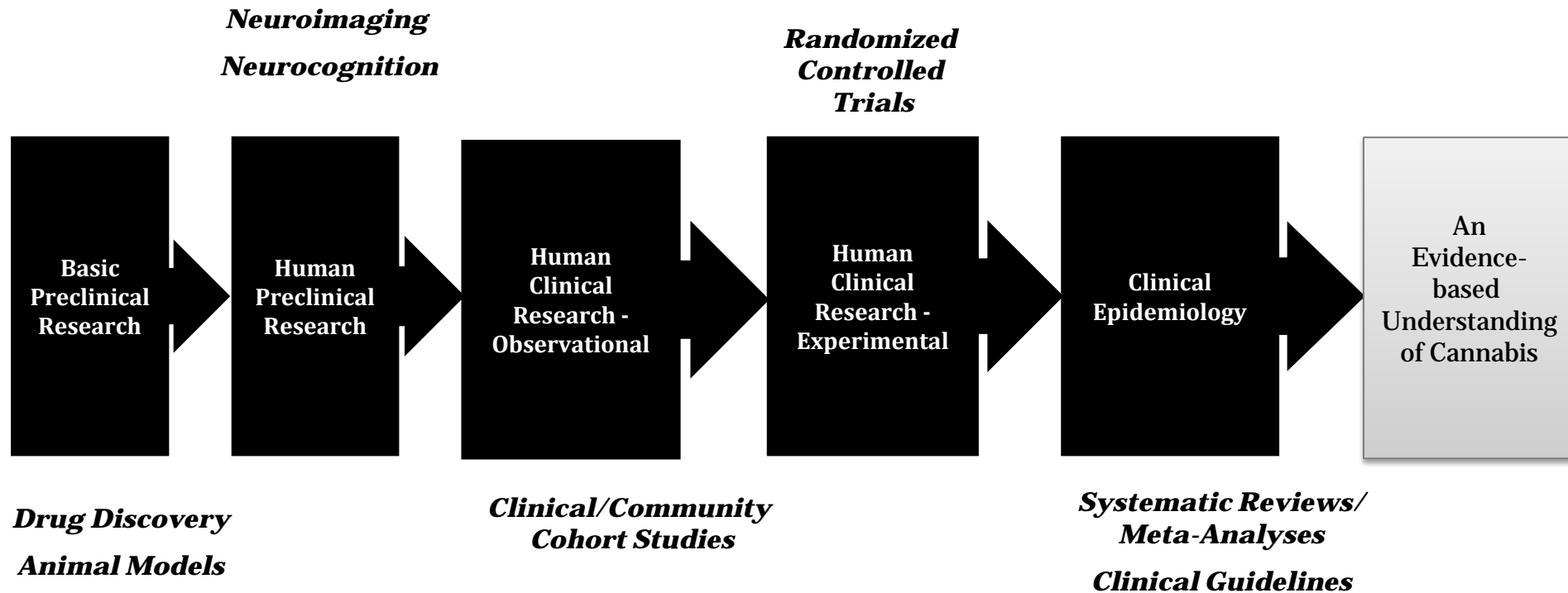


Overview:

- **40% of products were outside the variability limits for THC**
- **All products outside the variability limits were lower in THC than labelled (i.e., were over labelled) except for one which had more THC than labelled (i.e., was under labelled)**
- **Looking specifically at higher-potency products (≥ 2.5 mg/g THC), 44% were over labelled beyond 15%**

Doggett et al. (2024)
JAMA Network Open

Translational Framework



Basic Research on Cannabinoids and Health

McMaster researchers uncover hidden antibiotic potential of cannabis



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ACS Infectious Diseases > Vol 6/Issue 3 > Article

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LETTER | February 4, 2020

Uncovering the Hidden Antibiotic Potential of Cannabis

Maya A. Farha, Omar M. El-Halfawy, Robert T. Gale, Craig R. MacNair, Lindsey A. Carfrae, Xiong Zhang, Nicholas G. Jentsch, Jakob Magolan, and Eric D. Brown*

Basic Research on Cannabinoids and Health

The impact of oral cannabis consumption during pregnancy on maternal spiral artery remodelling, fetal growth and offspring behaviour in mice



Tyrah M. Ritchie,^{a,b,c} Emily Feng,^{a,b,c} Fatemeh Vahedi,^{a,b,c} Sofya Ermolina,^{a,b,d} Christian J. Bellissimo,^{b,e,f} Erica De Jong,^{a,b,d} Ana L. Portillo,^{a,b,c} Sophie M. Poznanski,^{a,b,c} Lauren Chan,^{a,b,c} Sara M. Ettehadieh,^{a,b,c} Deborah M. Sloboda,^{e,f,g,h} Dawn M. E. Bowdish,^{a,b,d} and Ali A. Ashkar^{a,b,c,*}



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^dFirestone Institute for Respiratory Health, St. Joseph's Healthcare, Hamilton, ON, Canada

^eDepartment of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, ON, Canada

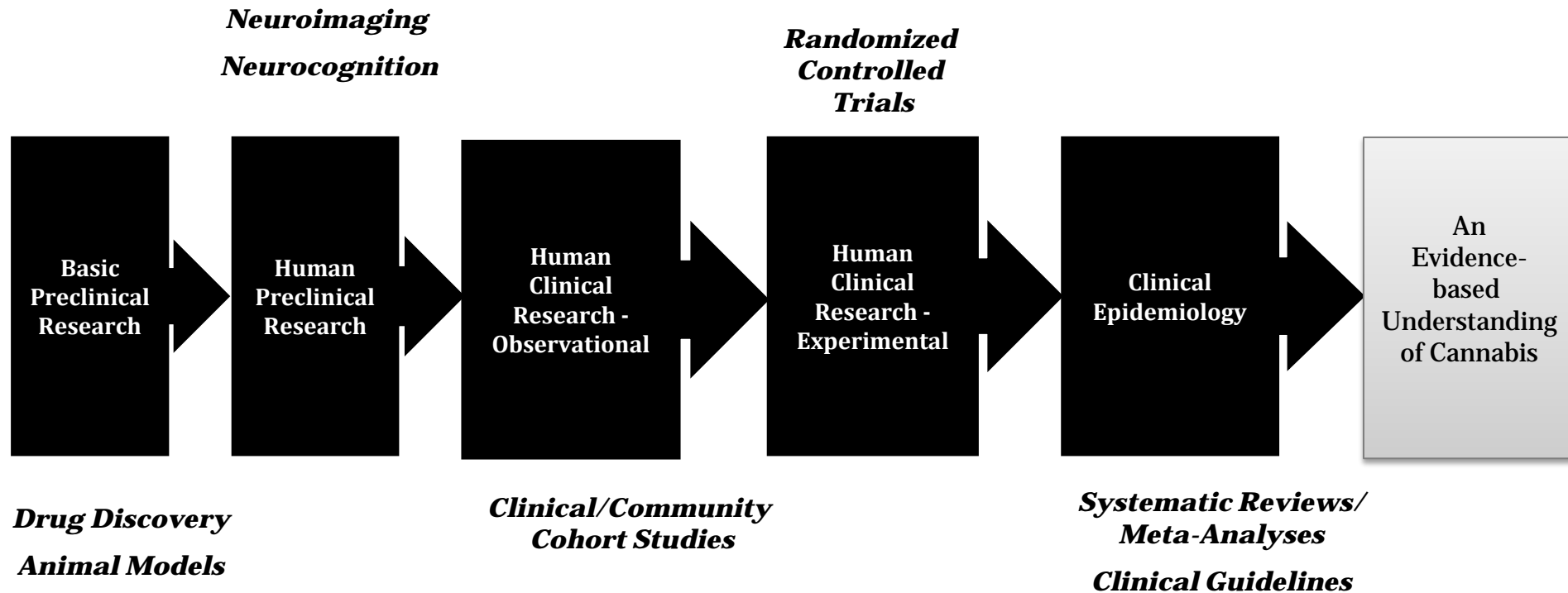
^fFarncombe Family Digestive Health Research Institute, McMaster University, Hamilton, ON, Canada

^gDepartment of Pediatrics, McMaster University, Hamilton, ON, Canada

^hDepartment of Obstetrics and Gynecology, McMaster University, Hamilton, ON, Canada

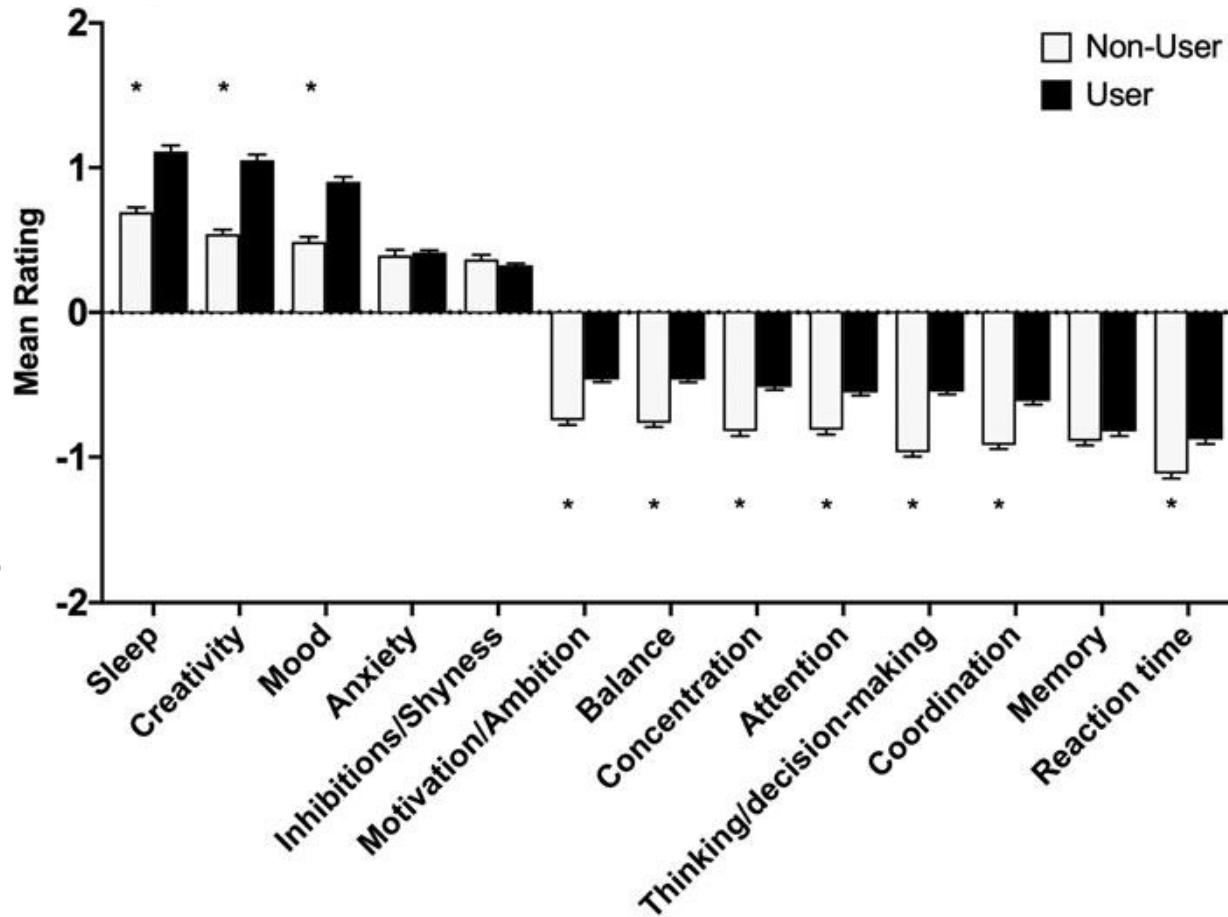
Findings We observed impaired maternal spiral artery remodelling in cannabis exposed mice and found that CBD and THC disrupt immune cell angiogenic factor production. Oral consumption of THC or CBD oil also resulted in significant fetal growth impairment and led to long-lasting sex-dependent consequences as male offspring exhibited altered aggression and metabolic activity while females had impaired spatial learning.

Translational Framework



Perceived Effects of Cannabis

Positive Effects



Negative Effects

Recent Empirical Findings

Neurocognitive Test	Cognitive Function	ΔR^2	p
Penn Word Memory Test	Verbal episodic memory	--	--
Flanker Task	Inhibitory Control	--	--
Dimensional Change Card Sort	Set Shifting	--	--
Short Penn CPT	Sustained Attention	--	--
Penn Progressive Matrices	Fluid Intelligence	.010	.004
Delay Discounting Tasks	Impulsive Choice Preference	--	--
Picture Sequence Task	Non-verbal Episodic Memory	.011	.004
Pattern Completion Task	Processing Speed	.014	.001
List Sorting Task	Working Memory	--	--
9-hole Pegboard Task	Psychomotor dexterity	--	--



Participants (N=1121): 53.4% female, M age = 28.83

THC+

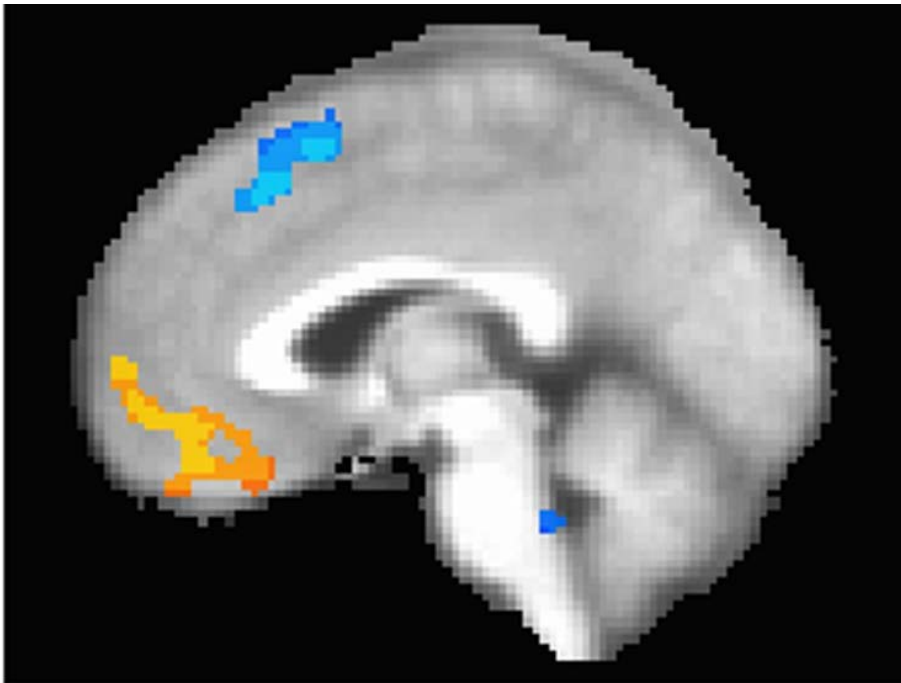
CUD+



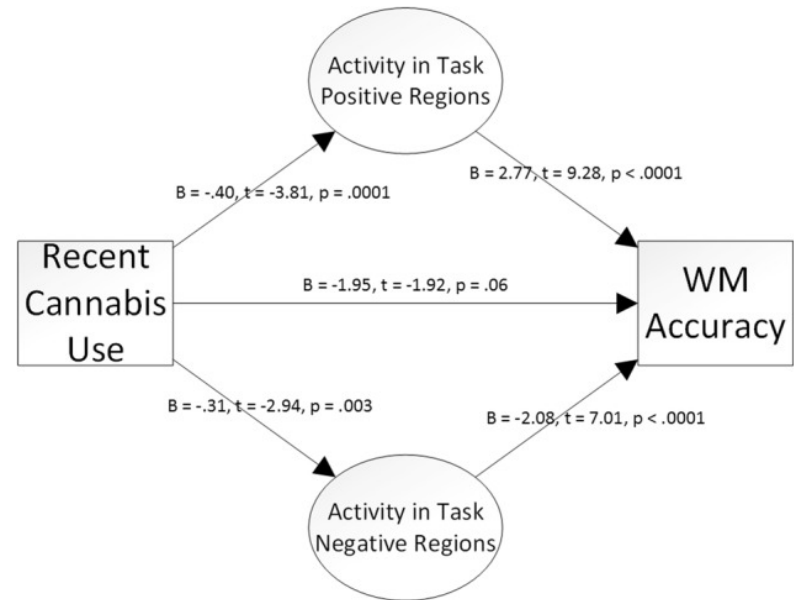
Petker et al. (2019)
Journal of Psychiatry & Neuroscience

Neuroimaging & Neurocognition

N-Back Performance (N = 1038)

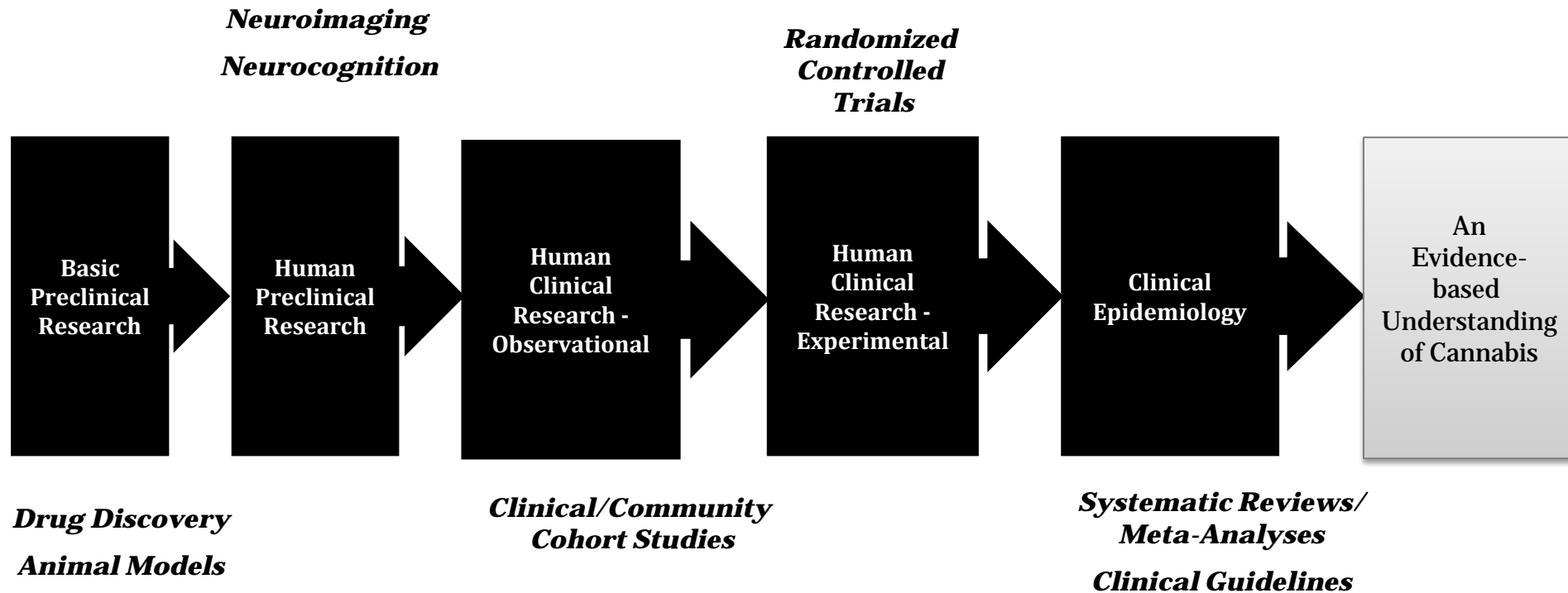


Blue = less activity during 2-back
Yellow = greater activity during 2-back

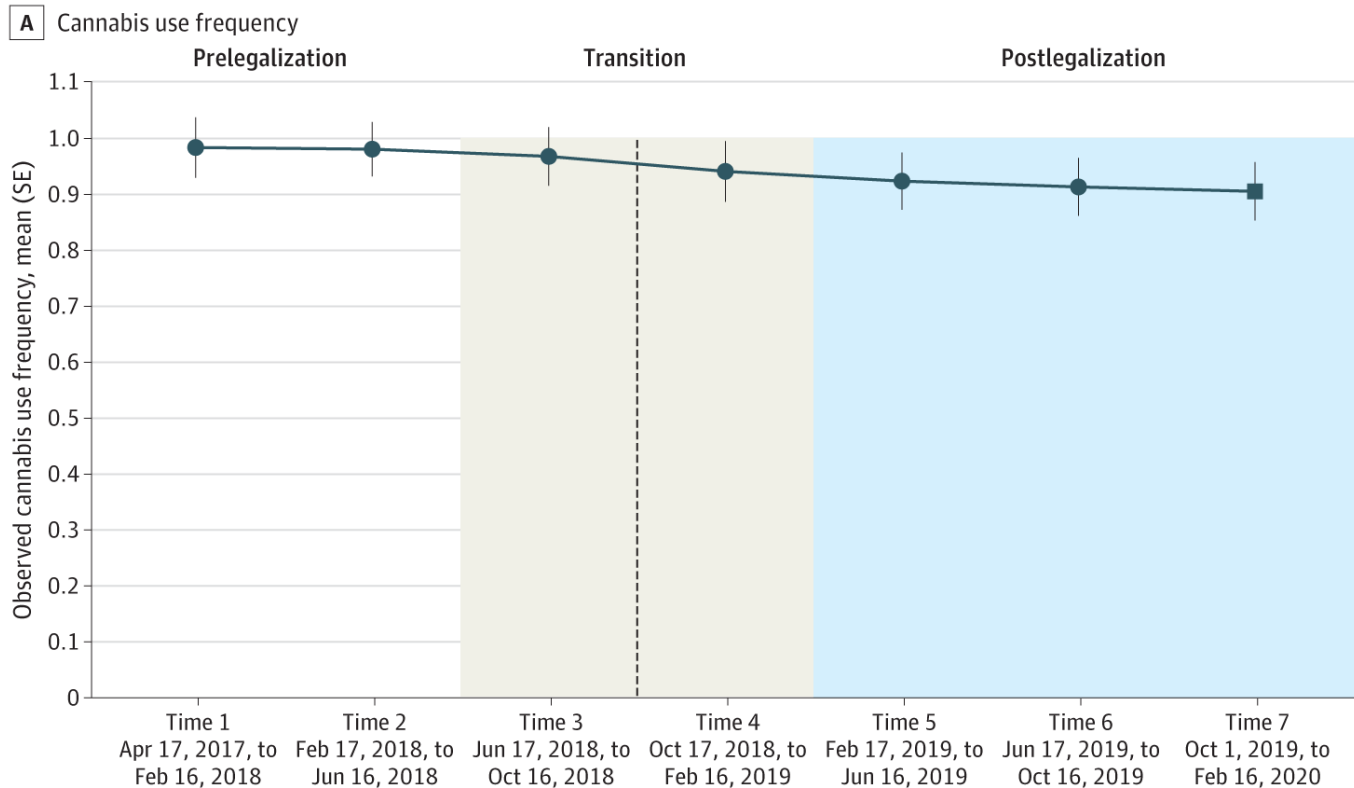


Owens et al. (2022)
Neuropsychopharmacology

Translational Framework

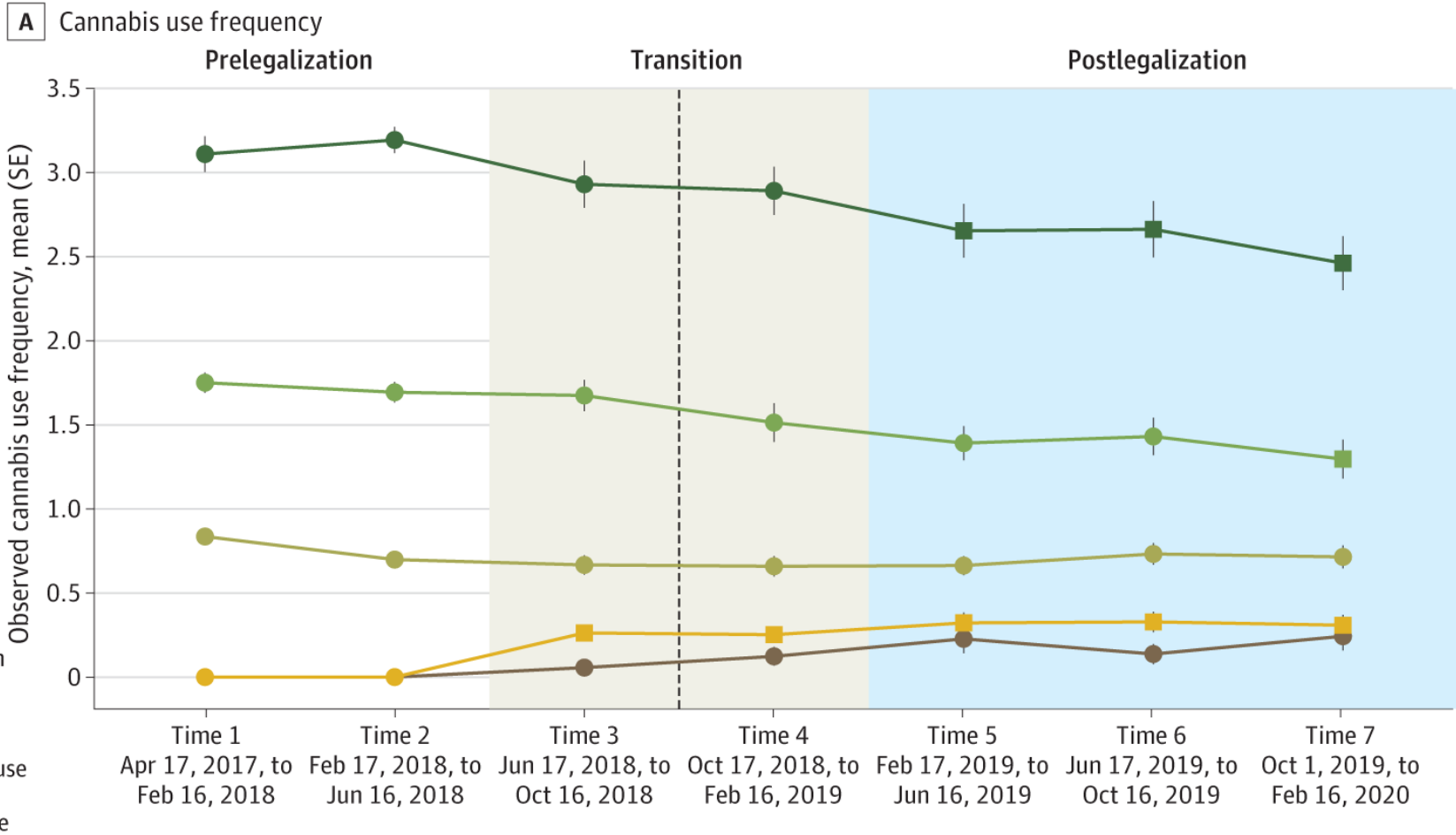


Observational Cohort Studies: High-risk Young Adults

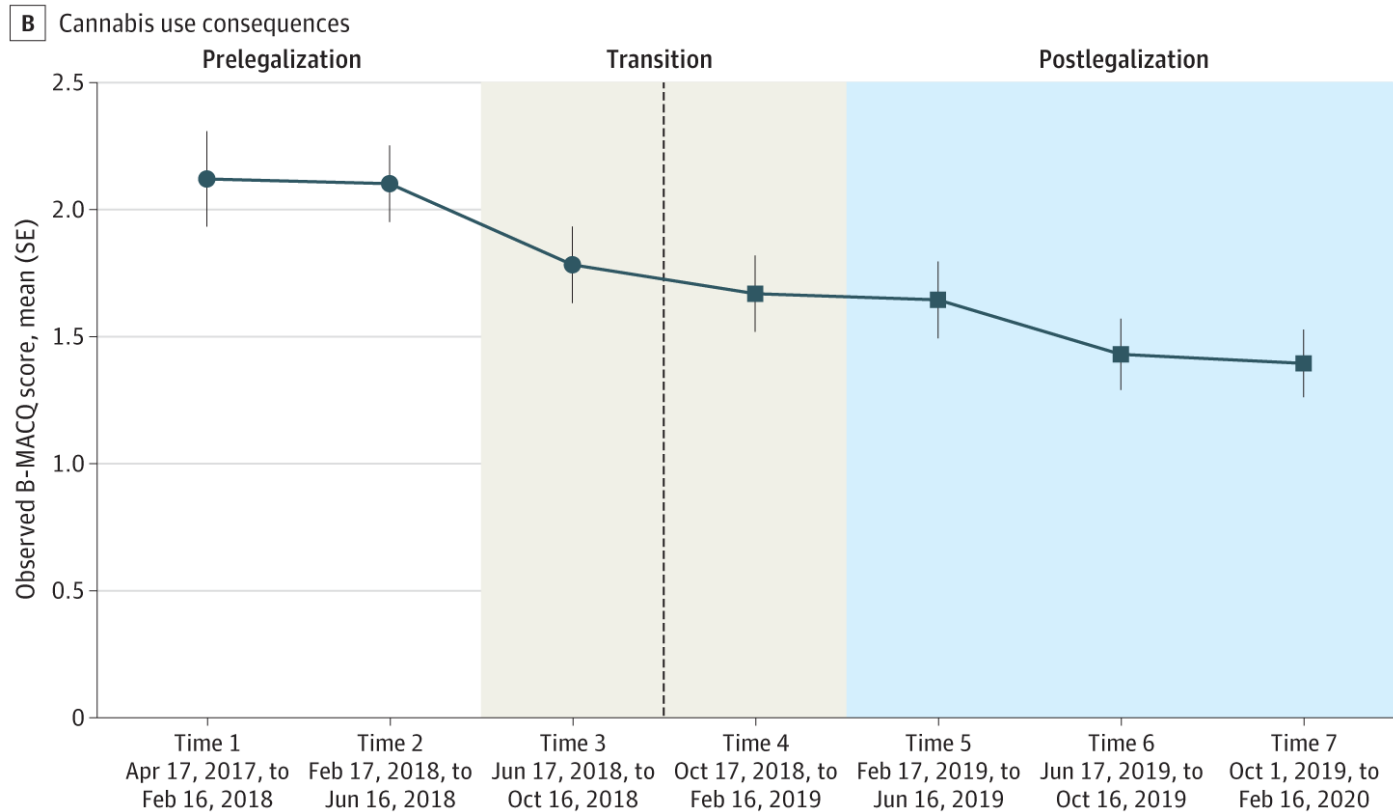


Doggett et al. (2023)
JAMA Network Open

Observational Cohort Studies: High-risk Young Adults



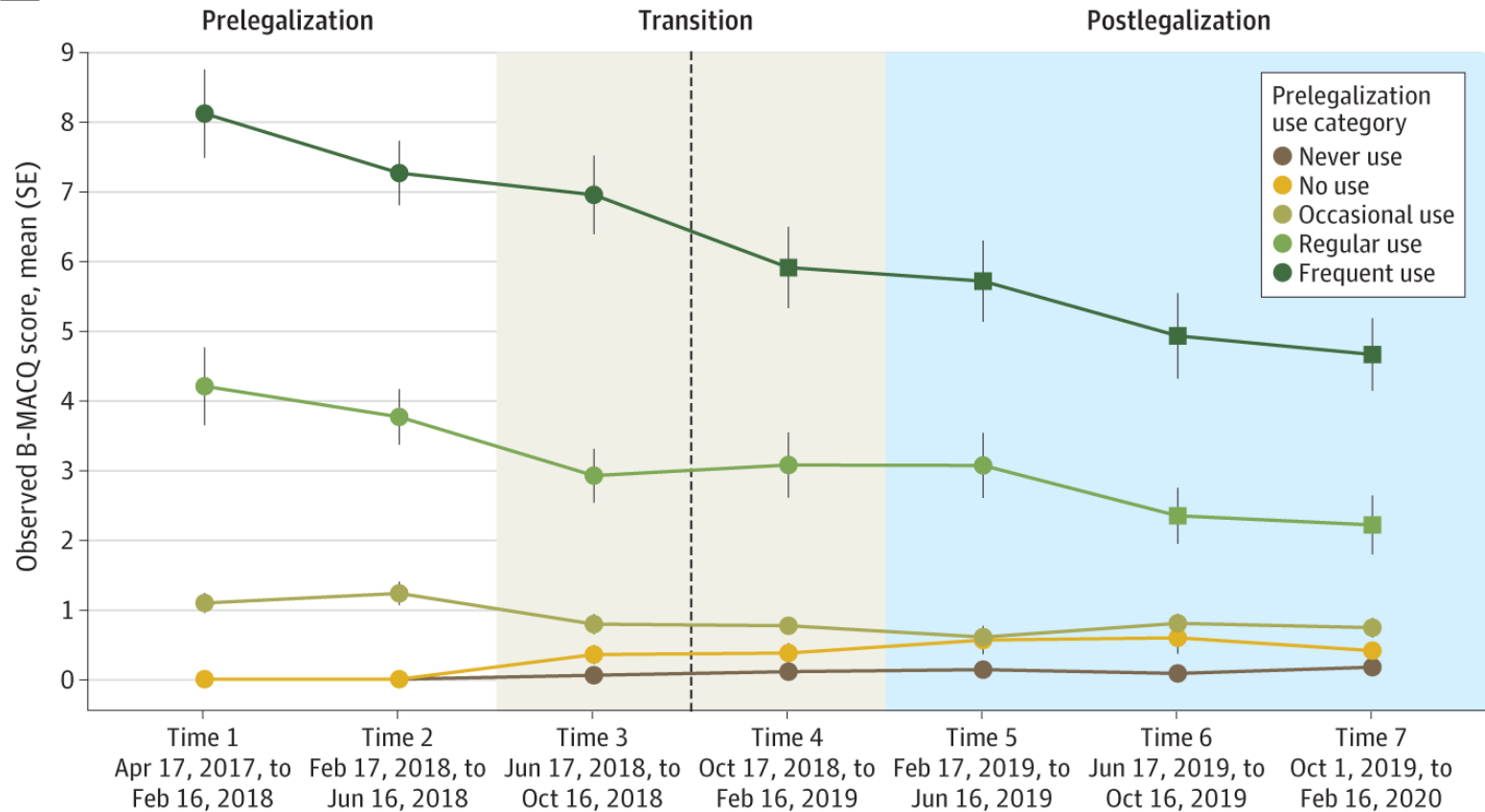
Observational Cohort Studies: High-risk Young Adults



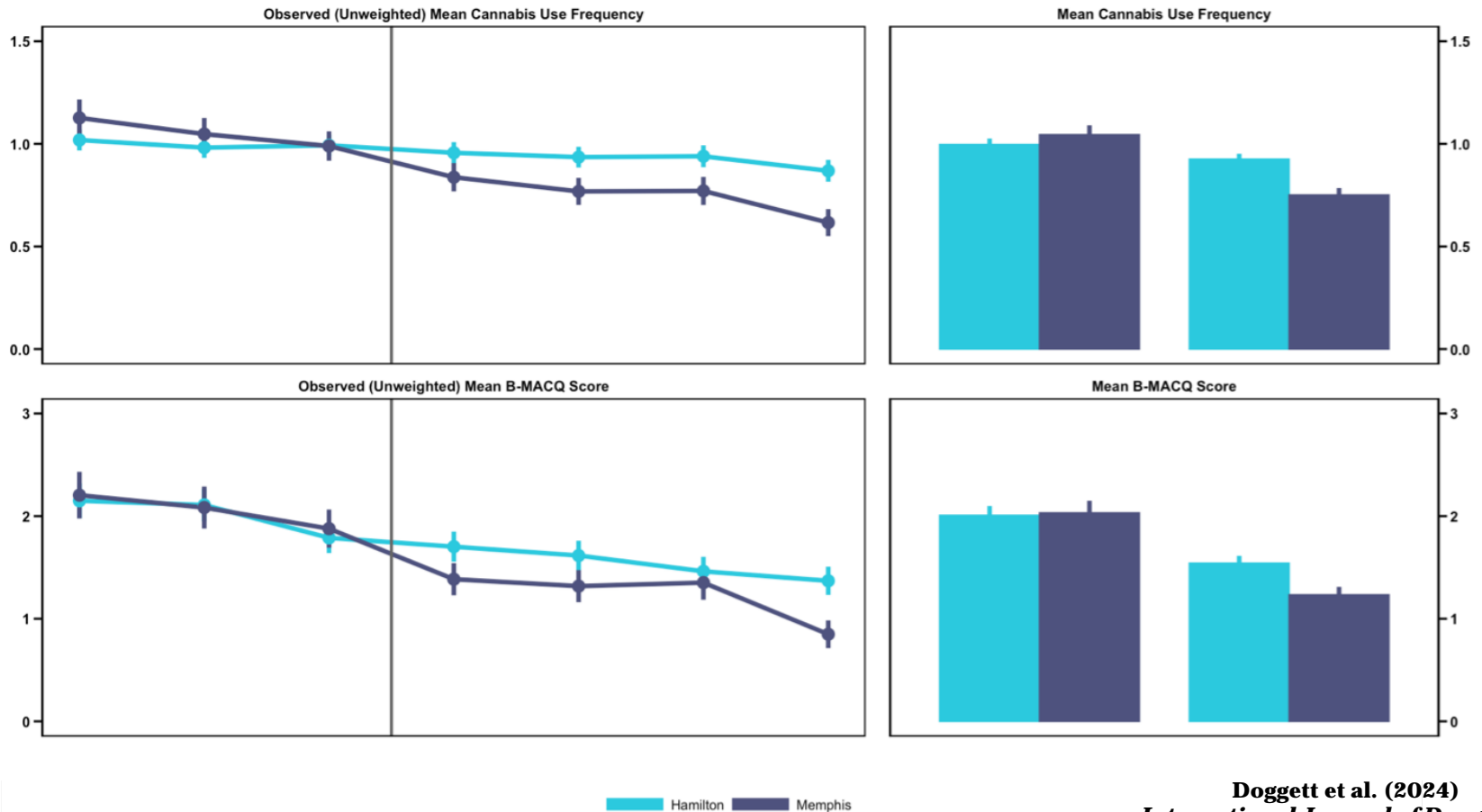
Doggett et al. (2023)
JAMA Network Open

Observational Cohort Studies: High-risk Young Adults

B Cannabis use consequences



Revisiting Changes using a Natural Experiment Design



Doggett et al. (2024)
International Journal of Drug Policy

Cannabis & Lung Health

Condition	Evidence	Mechanism	Quality of evidence
Bronchial Respiratory Symptoms	<i>Increased prevalence of chronic bronchial respiratory symptoms.</i>	Increased bronchial inflammation; basement cell hyperplasia, basement membrane thickening, goblet cell hyperplasia, loss of ciliated epithelium.	B
Lung Function and COPD	<i>No relationship found between development of COPD and cannabis smoking. No relationship with COPD exacerbations.</i>	No convincing evidence found that that cannabis inhalation leads to a decline in FEV1. However, cannabis smoking leads to an increase in airway resistance.	B
Asthma Control	<i>Cannabis smoking contributed to an increase in asthma risk and exacerbation rate.</i>	Modest, acute bronchodilator effect on CB1 and CB2 receptors. Increase prevalence of asthma in cannabis smokers. In known asthmatics, cannabis smoking independently increases the use of asthma medications.	A
Bullous Lung Disease and PNX	<i>Strong cannabis smoking is associated with bullous lung disease and spontaneous PNX.</i>	Deep inhalation and barotrauma, with significant fluctuations in endopleural pressure.	D (BLD) A (PSP)
Respiratory Infections	<i>Consistent correlation between cannabis smoking and susceptibility to infections, including Aspergillus, Legionella, and Tuberculosis. No increased risk of COVID19 infection</i>	Presence of potential biological contaminants and the immunosuppressive effect of cannabis, on both the innate and adaptive immune systems. This anti-inflammatory action could potentially compromise the host's immune response and contribute to the progression of the disease.	D
Interstitial Lung Disease	<i>Limited and sporadic evidence of association with ILD, with no causative link. Case reports on cannabis-related HP.</i>	Contaminants in cannabis, such as herbicides and heavy metals, could potentially contribute to the development of pulmonary fibrosis.	D
Lung Cancer	<i>Increased risk of lung cancer, notably even at a young age.</i>	Cannabis smoke contains numerous toxic substances and carcinogens. Significant rise in carboxyhemoglobin levels and increased accumulation of inhaled tar within the respiratory tract contribute to an intensified exposure to the carcinogens present in the cannabis smoke.	A
Acute Lung Injury (EVALI)	<i>Cannabis itself does not cause EVALI, but the majority of patients were using e-cigarettes containing cannabis products.</i>	The majority of BAL samples extracted from EVALI patients contained THC.	D

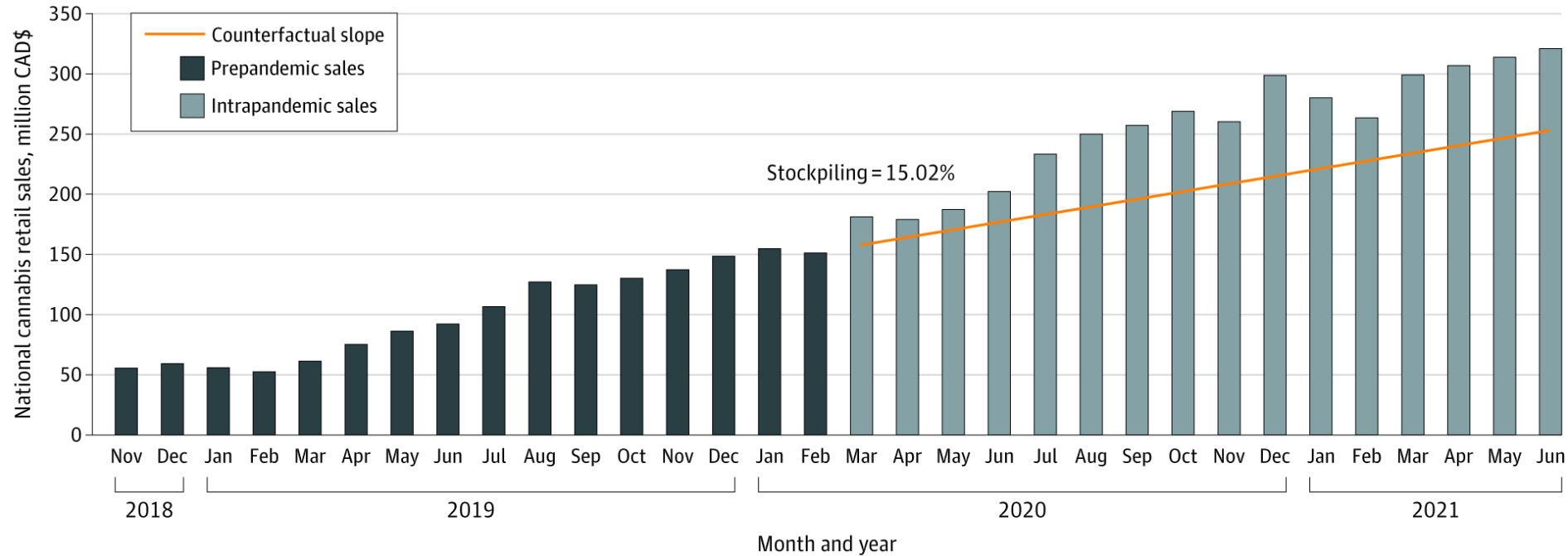
MGD CMCR Lung Laboratory

- Spirometry
- Oscillometry
- Fractional Expired Nitric Oxide (FENO)
- Expired CO
- Patient-reported Outcomes (SGRQ, CSQ)



Changes in Cannabis Sales

A Prepandemic and intrapandemic cannabis sales

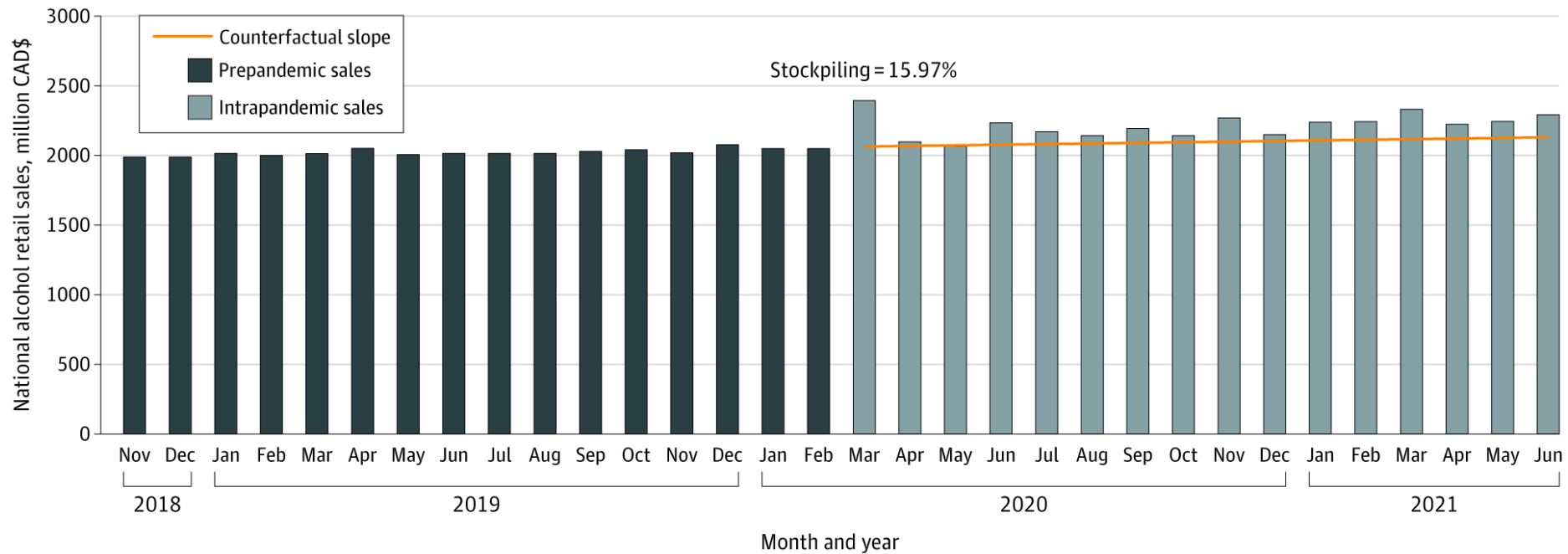


MacKillop et al. (2021)



Changes in Alcohol Sales

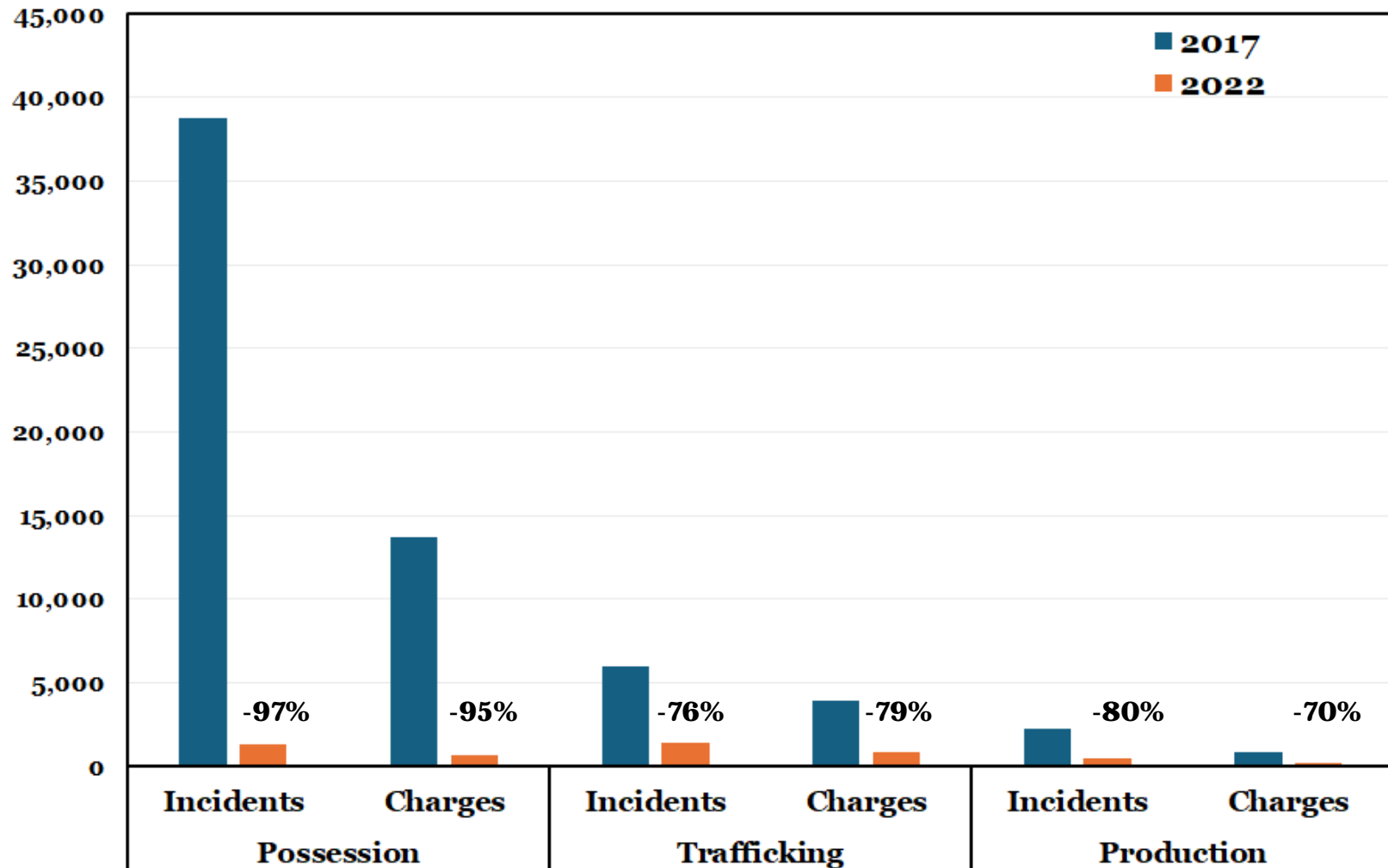
A Prepandemic and intrapandemic alcohol sales



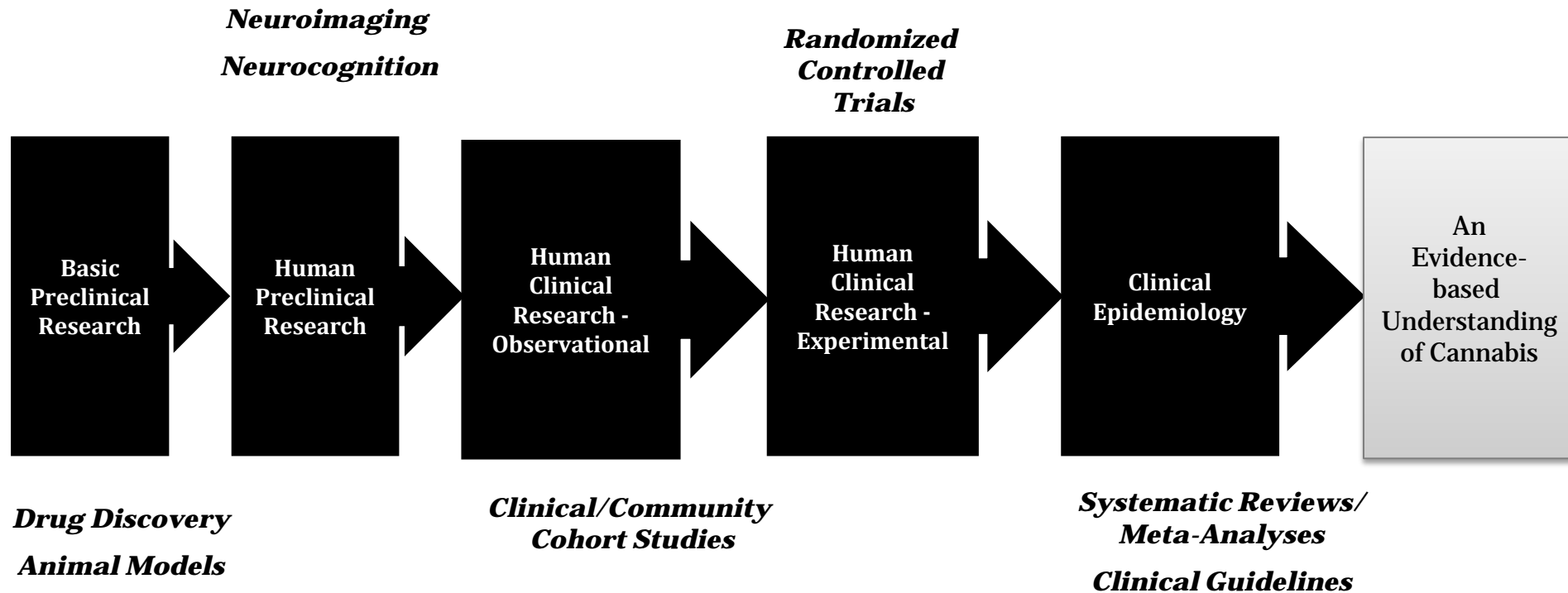
MacKillop et al. (2021)



Cannabis-related offences in 2017 and 2022



Translational Framework



Smoked cannabis for chronic neuropathic pain: a randomized controlled trial

Mark A. Ware MBBS, Tongtong Wang PhD, Stan Shapiro PhD, Ann Robinson RN, Thierry Ducruet MSc, Thao Huynh MD, Ann Gamsa PhD, Gary J. Bennett PhD, Jean-Paul Collet MD PhD

Table 2: Pairwise comparisons of the effects of four potencies of smoked cannabis on average daily pain

Potency, % of THC	Potency, % of THC, mean difference (95% CI)							
	0		2.5		6.0		9.4	
0	-	-	-	-	-	-	-	-
2.5	-0.13	(-0.83 to 0.56)	-	-	-	-	-	-
6.0	-0.09	(-0.78-0.60)	0.04	(-0.64 to 0.73)	-	-	-	-
9.4	-0.71	(-1.40 to -0.02)	-0.58	(-1.27 to 0.11)	-0.63	(-1.30 to 0.06)	-	-

Note: CI = confidence interval, THC = tetrahydrocannabinol.

Ware et al. 2010, CMAJ

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MAY 25, 2017

VOL. 376 NO. 21

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

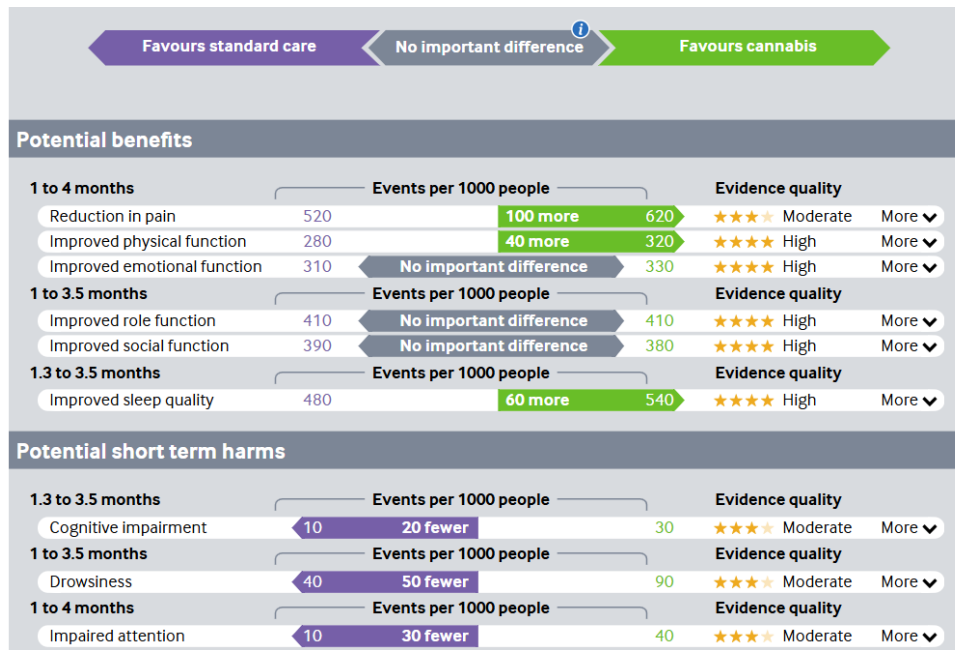
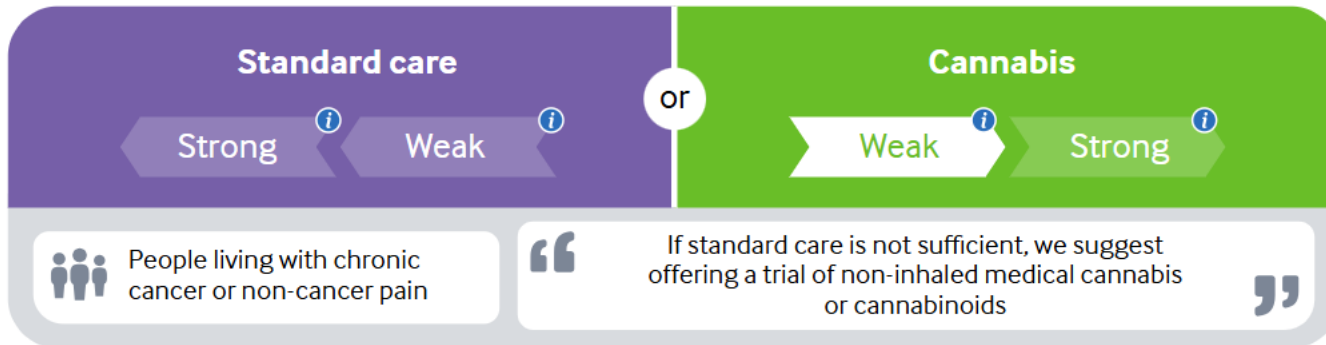
Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabhout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.*

Variable	Cannabidiol	Placebo	Adjusted Median Difference (95% CI) <i>percentage points</i>	P Value†
No. of convulsive seizures per mo — median (range)				
Baseline	12.4 (3.9 to 1717)	14.9 (3.7 to 718)		
Treatment period	5.9 (0.0 to 2159)	14.1 (0.9 to 709)		
Percentage change in seizure frequency — median (range)	-38.9 (-100 to 337)	-13.3 (-91.5 to 230)	-22.8 (-41.1 to -5.4)	0.01

Devinsky et al. 2017, *NEJM*

Cannabis for Pain Practice Guideline



Busse et al.
(2021) BMJ

Excessive Regulatory Burden for Clinical Trials

naturemedicine

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NEWS | 22 April 2021

Hundreds of scientists sign letter arguing that regulation is stifling cannabis research

Since the legalization of cannabis for recreational use in 2018, an expected boom in Canadian cannabis research has failed to happen, which has led scientists to demand changes in how clinical trials are regulated.

Canadian Medical Cannabis Clinical Trials Network (CMCN)



Dr. Jason Busse



Dr. James MacKillop



Dr. Lauren Kelly



Dr. Hance Clark



<https://www.cannabistrialsnetwork.ca/>

New Treatments for Cannabis Use Disorder



Medial Prefrontal Cortex (mPFC)



Lateral Prefrontal Cortex & Insula (IPFC + AI)



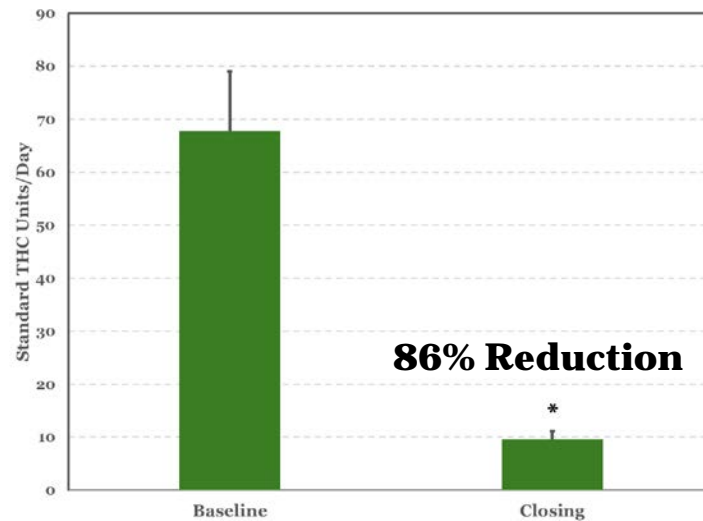
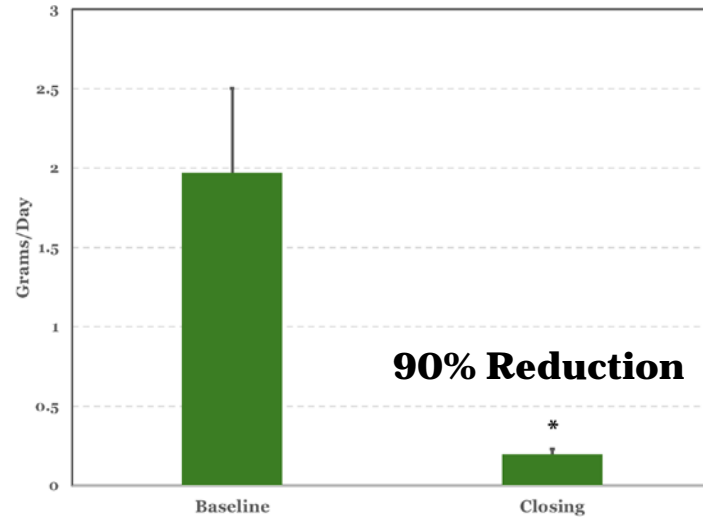
Anterior Cingulate Cortex (ACC)

New Treatments for Cannabis Use Disorder



H4-Coil

**PFC +
Insula**

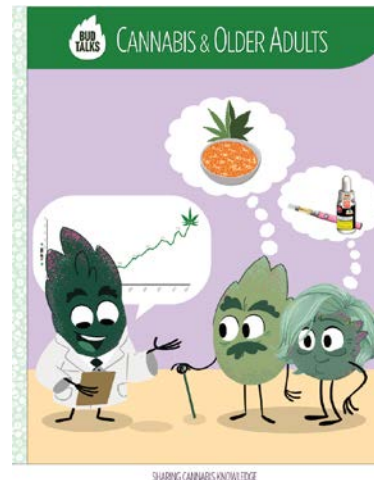


Cannabis Knowledge Translation

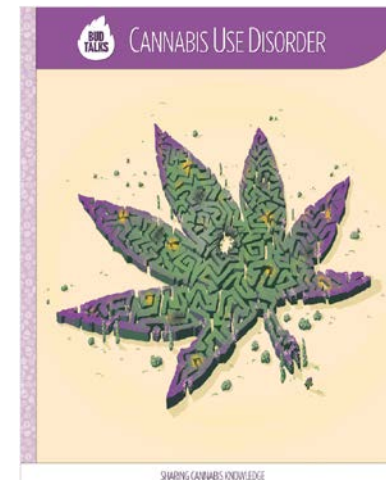
Cannabis Knowledge Translation



Dr. Iris Balodis
KT Lead



Cannabis & Seniors



Cannabis Use Disorder

www.budtalks.ca

Cannabis Knowledge Translation



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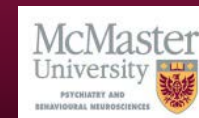
Promoting an evidence based understanding of Cannabis. ...more

cannabisresearch.mcmaster.ca and 2 more links

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<https://www.youtube.com/@MedicinalCannabisResearch>



Recapitulation and Conclusions

Thank You!



Michael G. DeGroote
CENTRE FOR MEDICINAL CANNABIS RESEARCH

