

Cannabis and the Developing Brain: What's the buzz about?



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Cannabis use in Canada: The sobering statistics



- Prevalence of use has significantly increased over last 20 years
- 12 million people (34% of population) have used in their lifetime
- Cannabis abuse/dependence rate greater than all other illicit drug abuse/dependence rates combined
- Canada's youth has the highest 12-month prevalence rate of cannabis use out of all developed countries (Adamson 2013)
- Almost 1 in 20 youth reported using cannabis daily or almost daily (Young 2011)

2013 Canadian Tobacco, Alcohol and Drugs Survey (CTADS)



Cannabis in Canada



National Academies of Sciences, Engineering, Medicine in *“The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research”* (January 2017) state:

....substantial evidence of a statistical association between cannabis and the development of schizophrenia or other psychosis

....moderate evidence of a statistical association between cannabis and increased incidence of suicidal ideation/attempts/completion

.... moderate evidence of a statistical association between cannabis and increased incidence of social anxiety disorders

.... moderate evidence of a statistical association between cannabis and increased incidence of increased mania/hypomania in individuals with bipolar disorder

(nationalacademies.org/CannabisHealthEffects)



Cannabis and Canada



Canadian context of:

- High rates and earlier onset of use
- Legalization of medicinal and recreational use (Bill C-45)
- Increasing availability and use of edible cannabinoid products
- Highly potent synthetic products available (e.g. Spice, K-2)
- Increasing potency of cannabis

Objectives

1. Understanding the potential outcomes of regular cannabis use during adolescence and young adulthood with a focus on psychosis
2. Appreciate the role of the endocannabinoid system on adolescent brain development
3. Appreciate the mental health community's role in knowledge translation in this area



What is the link between cannabis use and schizophrenia?



Epidemiologic Studies

- Longitudinal studies in the general population are necessary to examine the link between cannabis and psychosis
- Swedish conscript study (Andreasson 1987)
 - 45,570 conscripts followed up after 15 years
 - Those who smoked by the age of conscription had 2X the risk of developing schizophrenia (OR=2.3)
 - Findings confirmed in follow up of same cohort after 27 years
 - Dose-response relationship observed: heavy users were 6X more likely than non-users to develop schizophrenia (heavy use = used >50 times prior to age 18)



Epidemiologic Studies

Netherlands population-based prospective study (Van Os 2002)

- 4045 psychosis free at baseline, 1 year and 3 years.
- Cannabis at baseline 3X (adjusted OR=2.8) more likely to manifest psychotic symptoms at F/U
- Baseline cannabis history stronger predictor of psychosis outcome than use over the follow up period and use of other drugs



Epidemiologic Studies

Country	Study design	Sample size	Follow up	Odds Ratio (95% CI)
Israel (Weiser et al)	Population based	9,724	4-15 years	2.0
Netherlands (Ferdinand et al)	Population based	1,580	14 years	2.8
Germany (Henquet et al)	Population based	2,437	4 years	1.7
United Kingdom (Wiles et al)	Population based	8,580	18 months	1.5
Greece (Stefanis et al)	Birth cohort	3,500	NA	4.3

Epidemiologic Studies – Age of onset of use

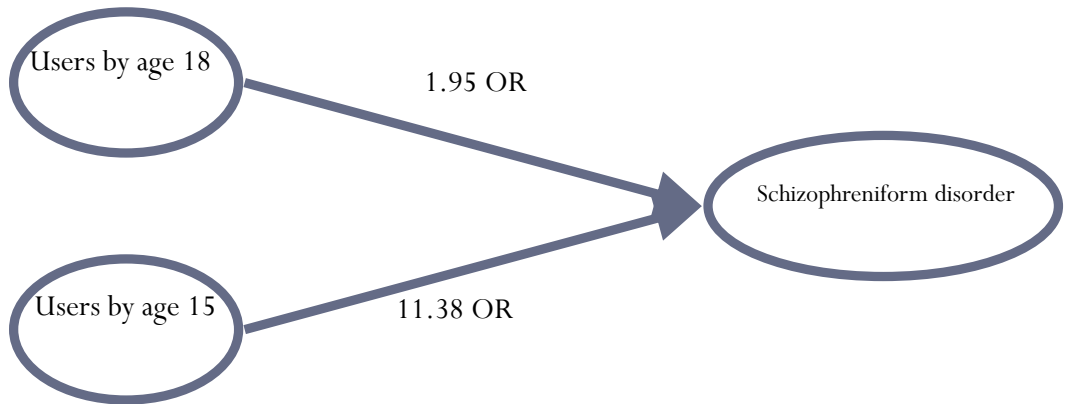
Epidemiologic studies have found that the **age of first use of cannabis** may be a key factor in the development of psychosis e.g. New Zealand Birth cohort study



- Ten evaluations of 1037 children from the age of 3.
- Quantification of drug consumption at 15 and 18 years of age.
- At age 26, 96% were interviewed using the Diagnostic Interview Schedule (DIS) for DSM-IV.

Arseneault L, et al. *BMJ*. 2002.

Cannabis users with schizophreniform symptoms by 26



Arseneault et al (2002); Casadio et al (2011)

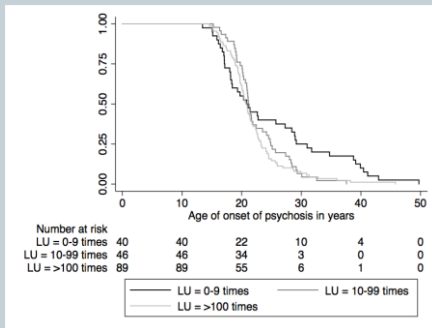
Epidemiologic Studies – Age of onset of use

- Mater-University Study of Pregnancy, Brisbane (McGrath 2010)
 - 7,223 women enrolled, 3801 of their children assessed at 21 years of age
 - Of the 3801 children, 228 sibling pairs
 - Longer use of cannabis associated with psychosis
 - This associated persisted when examined in sibling pairs
 - Those who had 6 or more years of use (thus starting at age 15 or younger) were 3X more likely to develop a non-affective psychosis



Cannabis and Age of Onset of Psychosis

Recent studies have also indicated that early cannabis use is associated with a decrease in the age of onset of schizophrenia (e.g. Sugranyes et al)



Dalhousie/Edmonton Study

- ▶ The extent of lifetime cannabis use was associated with earlier age of onset of psychosis (N=175)
 - Comparing those with lifetime 0-9 times use to those with more than >100 times, $p = 0.0381$

• Lodhi et al; *Brain and Behavior*, 2017



The New World Order: High Potency Cannabis

- The THC content of cannabis has increased over the years
- From one cannabis website:
 - *“The strongest strains are obviously those with the highest THC content. Generally speaking, anything that surpasses **20** % could be considered pretty potent. However, let’s say one grower’s harvest of Kosher Kush tested at 22 percent THC. Due to differences in environmental conditions, growing techniques, and genetic phenotypes, another grower’s Kosher Kush could come out wildly below the mark and test at, let’s say, 15 percent. Even with this variability, there are strains that tend to express higher levels of THC **thanks to strong genetics and selective breeding.**”*

The New World Order: High Potency Cannabis

- **Girl Scout Cookies; 28%**
- **Indica Kosher Kush; ‘always breaches 20%’**
- **Bruce Banner; ‘appropriately named after the Hulk’s alter ego, is a heavy-duty hybrid with a THC high-water mark of almost 29 percent. Rated the strongest strain in 2014 by High Times following its victory in the 2013 Denver Cannabis Cup, Bruce Banner has since carved itself quite the reputation. Powered by OG Kush and Strawberry Deisel genetics, Bruce Banner delivers a dizzying punch of euphoria that anchors your body in deep relaxation.’**
- **Ghost Train Haze; 25%**
- Death Star, Strawberry Cough, The White, Red Dragon, White Fire, Gorilla Glue

The New World Order: High Potency Cannabis

“Shatter”



“Wax”



- Typically use butane to extract oil.
- Very potent 80 to 90 % THC.
- THC:CBD ratio of product has also changed over the years

High Potency Cannabis and Psychosis

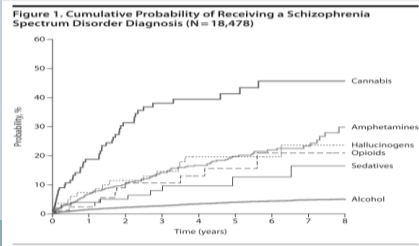
Di Forti; Lancet Psychiatry 2015

	Odds Ratio (95%CI)	Prevalence of exposure in FEP
Daily cannabis use	3.04 (1.91-7.76)	123/410 (30%)
Skunk use	2.91 (1.52-3.60)	218/410 (53%)
Daily Skunk use	5.40 (2.80-11.30)	103/410 (25%)

This has been more studied in Europe than in North America

- Incidence of psychosis differences has been observed in countries with/without use of high potency cannabis use (Hannah Jongsma et al; EU-GEI study)
- Cases of psychosis being reported with 'wax dabs' (e.g. Pierre et al)
- "spicephrenia"; symptoms due to synthetic cannabinoids (e.g. Papanti et al. Fattore et al)
- Daily users of high-potency cannabis experiencing their first symptoms of psychosis on average 6 years younger (Di Forti et al)

Niemi-Pynttari et al; J Clin Psychiatry 2013



Why a greater risk in those who start early?



Why a greater risk in those who start early?

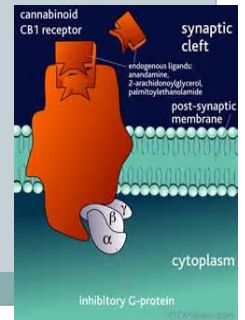
1. Reflects an increased propensity of young people with psychotic experiences to start cannabis use (reverse causality)
2. Higher cumulative exposure to cannabis in early users
3. Increased vulnerability to THC during critical phase of brain maturation

Endocannabinoid System



Endocannabinoid System

- Components of cannabis extracted and THC was elucidated to represent the psychoactive component in 1965 (Mechoulam et al)
- The isolation of THC resulted in characterization of a G protein-coupled receptor to which THC binds (CB1 receptor) in 1988 (Devane et al)
- 1990's CB1 was genetically determined and its distribution mapped in the brain
- We now know that CB1 receptor is one of the most abundant G-protein coupled receptors in the brain



Endocannabinoid System

- Presence of CB1 receptors suggested the existence of an endogenous substance that naturally binds to these receptors
- Endogenous ligands: **anandamide** and **2-AG** (synthesized by principal output neurons e.g. pyramidal neurons in hippocampus and cortex) reported in the 1990's
- Generated from phospholipid precursors in the neuronal membrane
- This system does not behave in the manner of most neurotransmitter systems

Endocannabinoid System

- Act presynaptically to inhibit the release of amino-acid neurotransmitters from neighboring GABAergic and glutamatergic neurons
- Thus regulate excitatory and inhibitory inputs

.....represents a critical player in the maintenance and determination of synaptic plasticity

.....plays a highly specialized and functionally distinct role during development that extends beyond the regulation of transmitter release

Endocannabinoid system and brain maturation



Gestational Period



- During early phases of neuronal development, endocannabinoid signaling is integral to:
 - Proliferation and differentiation of progenitor cells
 - Neuronal migration
 - Axonal guidance
 - Positioning of cortical interneurons
 - Neurite outgrowth

Gestational Period



Pharmacological blockade of the CB1 receptor in mid-late gestational periods

- Impaired progenitor proliferation
- Disrupted axonal pathfinding resulting in cortical delamination (Mulder et al)

In Utero exposure to THC

- Effects interneuron positioning (effects reported in hippocampus) (Berghuis et al)
- fetal failure to thrive (small for gestational age), reduced birth weight, pre-term delivery and increased risk of intensive care admission upon delivery
- Prenatal cannabis exposure also has shown to have effects on cognition and personality variables, as well as mood, reported in adolescent follow-up studies (reviewed in Jaques et al)

Adolescent Period



- Throughout adolescence a considerable degree of neuronal rearrangement occurs, including:
 - synaptic remodeling (pruning and development)
 - and enhanced connectivity (receptor distribution, volumetric growth, myelination)
- Cortex (PFC) and hippocampus develop later than other areas
- ***During adolescence, levels of endocannabinoids and expression of CB1 receptors increase, peaking in puberty (declines throughout adulthood)***
- Play a role in maturation of brain processes of cell proliferation, migration and differentiation; and influencing neurotransmitter system maturation

Endocannabinoids and brain maturation



Two points from this discussion:

1. Adolescence represents a period of heightened CB1 receptor density and possibly functionality, meaning that the effects of cannabis during this time could be fundamentally different than the effects on a mature brain.
2. There is compelling biological explanation for how cannabis exposure during adolescence could have adverse effects on brain development and function, particularly that of the PFC and white matter (WM)



Evidence that cannabis use in adolescence can affect brain structure and function

Adolescent cannabis use and the brain



- Learning and memory deficits, reduced attention (persists following abstinence)
- Reduced ability to process and regulate emotions
- Alexithymia 2X level seen in comparison cohort

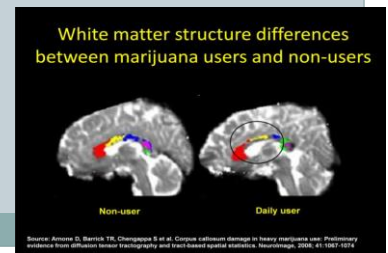
MRI:

- hippocampal and amygdala volume reductions (some studies indicate volumes inversely related to length of exposure)
- Gyrfication abnormalities
- Use before 17 yrs: smaller whole brain and percent cortical grey mater

White Matter in adolescent cannabis use

CB1 receptors are present on astrocytes, microglia, and oligodendrocytes

- Decreased DTI FA in genu of corpus callosum and left internal capsule (mean age 23 yrs) (Gruber et al)
 - Younger age of onset associated with greater severity of WM disruptions
- WM abnormalities (connectivity maps) in splenium of CC and R fimbria (mean age 33 yrs) (Zalesky et al)
 - Onset prior to age 16 driver of severity of change



Neuroimaging reviews in Psychosis:



1) *Effects of Cannabis Use on Human Brain Structure in Psychosis: A Systematic Review Combining in vivo Structural Neuroimaging and Post Mortem Studies.* (Rapp et al 2012).

- 15 structural (12 cross sectional, 3 longitudinal), 4 post mortem. [6 FEP studies]
- Brain structural abnormalities in CB1 receptor rich areas such as the cingulate, prefrontal cortex, and cerebellum.
- Rais et al longitudinal study; C+ FEP, C- FEP and C-HC at baseline and 5 years

2) *Cannabis Abuse and Brain Morphology in Schizophrenia: A Review of the Available Evidence.* (Malchow et al 2013)

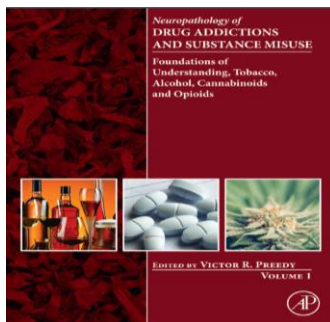
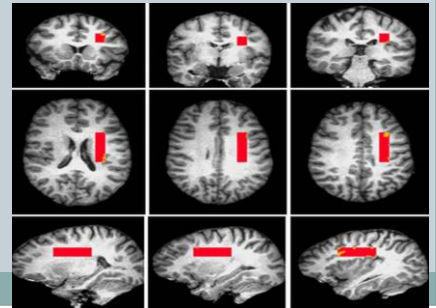
- 16 studies reviewed (8 FEP, 3 EOS studies)
- Heterogeneity of definitions, methods, and sample sizes
- Studies using FEP populations most robust to show influence of cannabis on brain structure apart from effects of schizophrenia itself.

Recent neuroimaging reviews in Psychosis:



3) *White matter changes in early phase schizophrenia and cannabis use: An update and systematic review of diffusion tensor imaging studies.* (Cookey et al 2014)

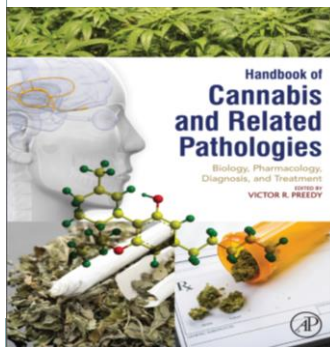
- Exclusion criteria included studies that did not control for alcohol or other illicit drug use, or sample size <20.
- Widespread WM disruption including the association, callosal, projection, and brainstem fibers



Chapter 79

White Matter, Schizophrenia, and Cannabis

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CHAPTER

36

Neuroimaging Findings in Adolescent Cannabis Use and Early Phase Psychosis

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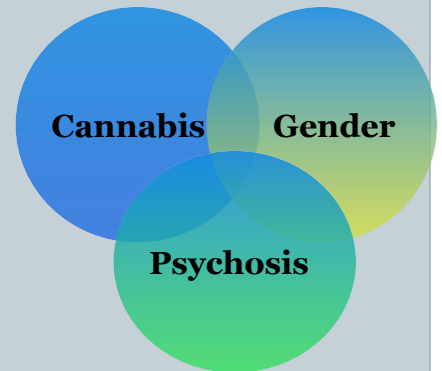
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Cannabis use and negative outcomes in psychosis

Persisting comorbid cannabis abuse is associated with:

- Increased severity of symptomatology
- Lower medication compliance
- Higher relapse rates (first episode psychosis)
- More frequent and longer hospitalizations
- Elevated rates of EPS
- Higher rates of unemployment, criminality
- Increase risk of suicide
- Gender differences
 - *“The Interaction of Gender and Cannabis in Early Phase Psychosis”*
Crocker and Tibbo, Schizophrenia Research 2017



Interventions in FEP Services

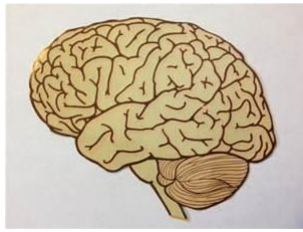
Psychosocial Interventions in Reducing Cannabis Use in the Early Psychosis: A Canadian Survey of Treatments Offered

Aydin C, Tibbo P, Ursuliak Z. CJP 2016 Jun;61(6):367-72

- 32% of Canadian Early Psychosis Programs surveyed have formal addiction services (individual and group MI, CBT, and psychoeducation for patients/families).
- 82% of Canadian Early Psychosis Programs surveyed have informal addictions services (individual and group psychoeducation, individual MI and information resources).
- Surveys Sent: 31
- Response Rate: 71%



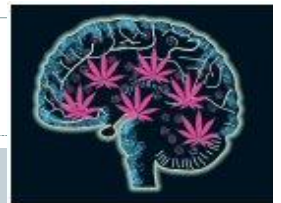
Another Variable to Consider in Psychosis Development



+ ? +



→ Psychosis



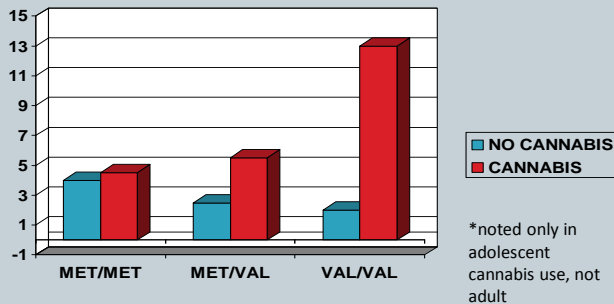
The majority of teenagers who use cannabis do not develop psychosis

- this suggests there may be additional factors that render the adolescent brain more sensitive to effects of cannabis in those that go on to develop psychosis
- {there are other outcomes though other than psychosis}

Gene x environment interactions

Defining Catechol-O-methyl-transferase (COMT) study

- ▶ Caspi *et al.* (2005) reported an association between the *COMT* Val158Met variant and schizophreniform disorder at age 26 years
 - ▶ Val carriers had a 10-fold increased risk (OR 10.9, CI 2.2-54.1) if they used cannabis during adolescence
 - ▶ Defined as first use before age 15 years or monthly use before 18 years
 - ▶ Individuals that had one copy of the Val had a two and a half-fold increased risk (OR 1.5, CI 0.78-8.2)

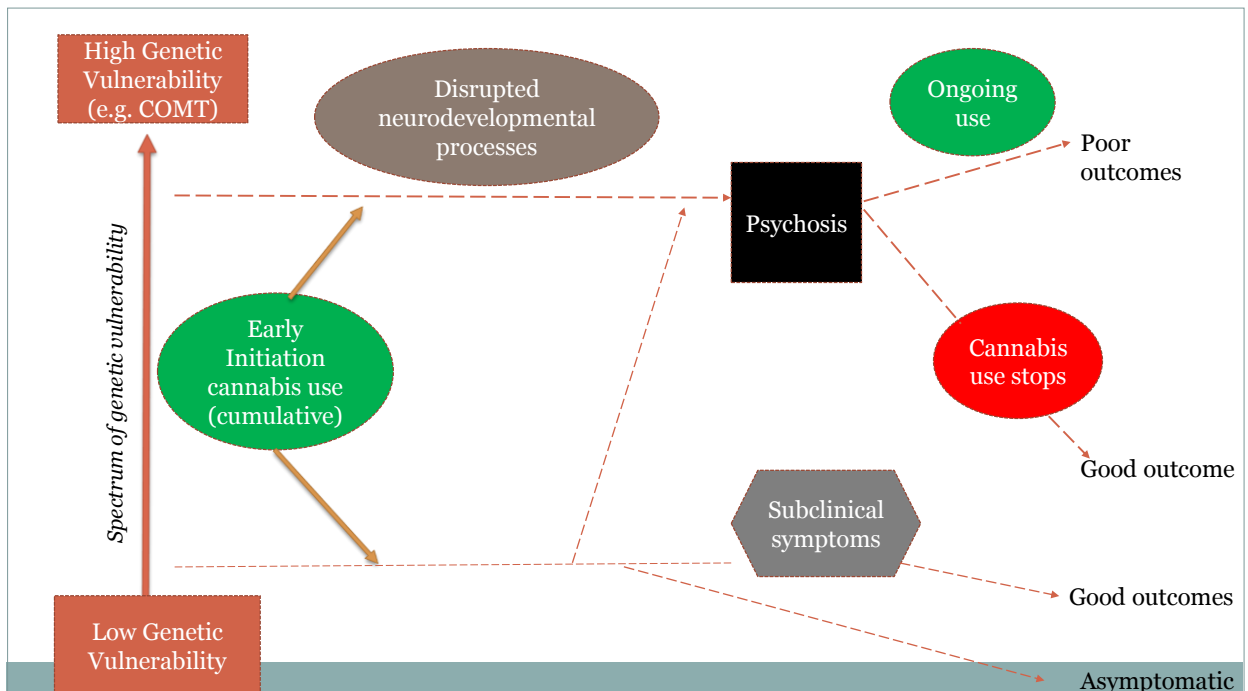


Edmonton/Halifax Study:

- ▶ *COMT* Val/Val was a predictor of earlier age of onset of psychosis in those who had first used cannabis before 20 years
- Lohdi *et al*; *Brain and Behaviour* 2017

Other genes of interest:

AKT1
DRD2



Our Role in Knowledge Translation?

- Position statements/papers
 - E.g. CMA, CPA
- Community presentations/panels
 - E.g. Canadian Center on Substance Abuse (CCSA)
- Educating parents
 - E.g. Drug Free Canada Kids (drugfreekidscanada.org)
- Educating youth
 - “WeedMyths” campaign in NS
 - Cannabis and Psychosis (CCEIP, endorsed by SSC and EPION)

Is there an opportunity for the scientific and clinical community to educate and be involved in public awareness?

Our Role in Knowledge Translation and Mental Health Advocacy? Educating Youth (in mental health care)

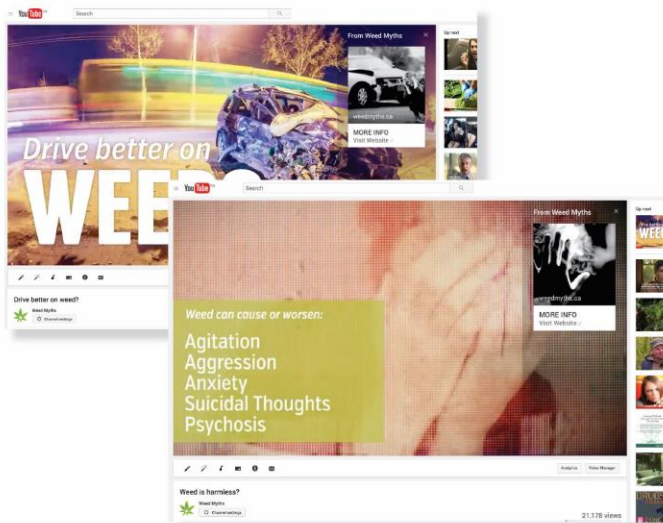
The collage features several key components:

- Logos:** EPION (Early Psychosis Intervention Network) and the Canadian Consortium for Early Intervention in Psychosis.
- Top Left:** Text describing the Canadian Consortium for Early Intervention in Psychosis as a national and bilingual organization of clinicians and researchers.
- Top Center:** A graphic titled "CANNABIS USE" with a list of slang terms: POT • WEED • CHRONIC • GREEN • KUSH • BUD • HERB.
- Top Right:** A section titled "WHAT MOTIVATES YOU TO USE POT?" showing various reasons like "Stress", "Socialize", "Relaxation", "Mood", "Taste", and "Taste of Weed".
- Middle Left:** A section titled "PEOPLE WHO ARE AT HIGH RISK FOR CANNABIS" listing related health problems such as anxiety, depression, and psychosis.
- Middle Right:** A section titled "CANNABIS IN CANADA" with icons for "Legal", "Medical", and "Recreational" use, and a note: "You will need a proper I.D.".
- Bottom Left:** A section titled "KNOW WHAT YOU ARE GETTING" comparing THC (Tetrahydrocannabinol) and CBD (Cannabidiol).
- Bottom Center:** A section titled "RISK OF PSYCHOTIC SYMPTOMS" showing a graph of "HIGH CANNABIS USE" leading to "PSYCHOSIS ONSET". It includes a statistic: "A 44% increase in psychosis risk for those who use high cannabis use compared to those who do not." and "30% of those who use high cannabis use experience psychosis symptoms.".
- Bottom Right:** A section titled "CANNABIS AND PSYCHOSIS" with a graph showing "CANNABIS USE" and "PSYCHOSIS RISK" over time. It states: "CANNABIS USE INCREASES SYMPTOM AND FUNCTION IN PATIENTS WITH SCHIZOPHRENIA".
- Far Right:** A section titled "CANNABIS: KEEP THIS IN MIND" with several safety icons: "AVOID USING CANNABIS", "WAIT UNTIL YOU'RE OLDER BEFORE USING CANNABIS", "DON'T USE SYNTHETIC CANNABIS", "IF USING, CONSIDER HIGH-DOSING METHODS", "AVOID INHALING TOO DEEPLY", "CHOOSE CANNABIS WITH LOWER THC LEVELS", "DON'T DRIVE WHILE HIGH", and "DON'T USE CANNABIS EVERYDAY".

Our Role in Knowledge Translation and Mental Health Advocacy? Educating Youth (in general)

- **WeedMyths public awareness and education campaign**
 - Funded by the MHFNS, NSEPP, NS DOHW
 - Creative team working with focus groups of youth and young adults
 - “Don’t ‘tell’ us what not to do”; no print, Instagram and YouTube with short ‘graphic’ videos
 - Campaign included bus shelter ads, Instagram and Youtube videos, website (WeedMyths.ca); recently expanded to include hockey rink and billboard
 - Focused on 2 myths (due to budget):
 - ✦ Drive better on weed
 - ✦ Weed is harmless
- **2 Runs of this campaign**

ONLINE CAMPAIGN YOUTUBE VIDEOS



2 YouTube Videos

50% of advertising budget

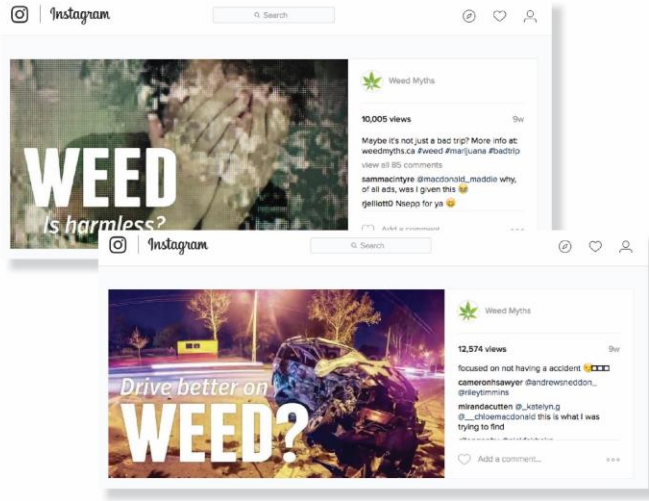
Paid targeting to 13-24 year olds within HRM

60 day campaign

Total impressions: 114,323

Total full video plays: 26,255

ONLINE CAMPAIGN INSTAGRAM VIDEOS



2 Instagram Videos

6% of advertising budget

Paid targeting to 13-24 year olds within HRM

60 day campaign

Total views: 22,578





OUTDOOR CAMPAIGN BUS SHELTER POSTERS



PRINT CAMPAIGN POSTCARDS

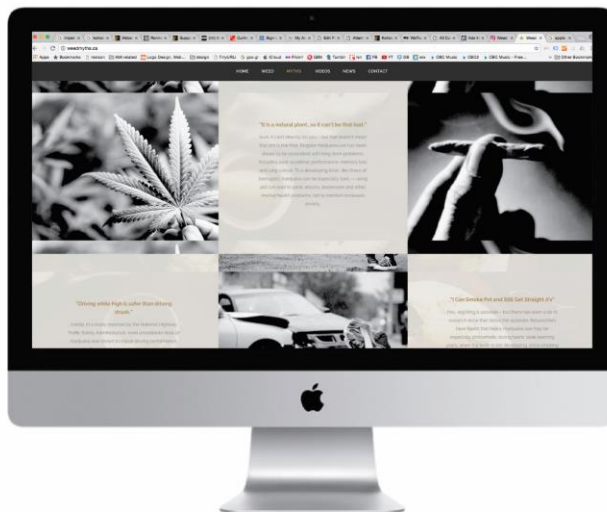


2 postcard designs

5% of advertising budget

Short run distributed to health care sector

ONLINE WEEDMYTHS.CA WEBSITE



Website creation to supplement advertising

All online ads contained links to the site

Contains additional information and research articles

Total views to date: 4,035

2nd Run (60 day) of Campaign

- **Started April 1, 2018**
- **YouTube**
 - Locations: Halifax, NS Valley region, Antigonish, Sydney
 - “Bad Trip”: 19,900 impressions, 7,400 views
 - “Drive Better”: 21,200 impressions, 8,600 views
- **Instagram**
 - “Bad Trip”: 36,300 impressions, 9,100 views
 - “Drive Better”: 49,800 impressions, 12,700 views
- **Bus shelter**
 - Halifax April 15 start
 - NS Valley region April 1 start
- **Hockey rink advertising**
 - Sydney x 2, Antigonish x 2, Wolfville, Kentville, Berwick x2, Kingston, Middleton
- **Billboard (Sydney)**

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