Cannabis and Psychosis: What’s the buzz?

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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/dependence 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)
What Canadian Youth Think about Cannabis

- 12 focus groups conducted during the summer 2012 with 76 youth age 14-19 across Canada (www.ccsa.ca)

- Youth often talked about cannabis as natural and not seen as a drug
- Mistaken beliefs about effects (e.g. can treat cancer)
- Confusion about legality and medical use
- Mixed belief whether improves or impairs driving
- Seen as less serious than drunk driving
3 year project funded by Health Canada – the Drug Strategy Initiatives fund of Health Canada

Lit review and environmental scan found little information for youth about cannabis and psychosis

Lack of youth-friendly information to help vulnerable youth become well-informed about this important issue.

The aim of the project: to increase awareness and understanding of the relationship between cannabis use and psychosis from the perspective of youth
Worked with 3 EI clinics across Canada to implement project
At each site, youth were trained as researchers (N = 28), asking their peers about their experiences with cannabis and psychosis (50 youth interviewed)

Results
- Theme 1” The ‘ups and downs’ of the experience
- Theme 2: Attributions for Initiation of Cannabis Use
- Theme 3: Cannabis and its Perceived Role in Illness

Website: cannabisandpsychosis.ca
Is there a 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
    - Does-response relationship observed: heavy users were 6X more likely than non-users to develop schizophrenia (heavy use = used >50 times prior to age 18)
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
<table>
<thead>
<tr>
<th>Country</th>
<th>Study design</th>
<th>Sample size</th>
<th>Follow up</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israel (Weiser et al)</td>
<td>Population based</td>
<td>9,724</td>
<td>4-15 years</td>
<td>2.0</td>
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<tr>
<td>Netherlands (Ferdinand et al)</td>
<td>Population based</td>
<td>1,580</td>
<td>14 years</td>
<td>2.8</td>
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<tr>
<td>Germany (Henquet et al)</td>
<td>Population based</td>
<td>2,437</td>
<td>4 years</td>
<td>1.7</td>
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<tr>
<td>United Kingdom (Wiles et al)</td>
<td>Population based</td>
<td>8,580</td>
<td>18 months</td>
<td>1.5</td>
</tr>
<tr>
<td>Greece (Stefanis et al)</td>
<td>Birth cohort</td>
<td>3,500</td>
<td>NA</td>
<td>4.3</td>
</tr>
</tbody>
</table>
Epidemiologic studies have found that the *age of first use of cannabis* may be a key factor in the development of psychosis.

- Two birth cohort studies from New Zealand
- Christchurch study (Fergusson et al)
  - Cannabis dependence at age 18 had 2X increased risk of psychosis compared with those without cannabis dependence
  - Statistically able to control for causation ie psychotic symptoms did not cause cannabis use
Epidemiologic Studies – Age of onset of use

- 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.

Cannabis users with schizophreniform symptoms by age 18 and age 15.

- Users by age 18: 1.95 OR
- Users by age 15: 11.38 OR

Ref: 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
Epidemiologic Studies – Age of onset of use

Dutch adolescent study (Schubert 2010, 2011)
- 18,000 adolescents administered an online version of the Community Assessment of Psychic Experiences (CAPE)
- Cannabis use at age 12 strongly associated with a score in the top 10% on psychotic experiences (OR 3.1)
- Early (under 12 years of age) and heavy use (>25 euro/week) were strongly and independently associated with an increased risk of psychiatric hospitalization
- Depressive symptoms not found to be associated with young age of cannabis use
Recent studies have indicated that early cannabis use also associated with a decrease in the age of onset of schizophrenia (e.g. Sugranyes et al)

Presented at ACNP annual meeting December 2014

- 204 subjects recruited between Halifax and Edmonton
- gender and age at regular use of cannabis were significant predictors of age at diagnosis (p=0.042 and p=0.035 respectively)

Why greater risk in those who start early?
Why 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
- *...and as such represents a critical player in the maintenance and determination of synaptic plasticity*
- *...also plays a highly specialized and functionally distinct role during development that extends beyond the regulation of transmitter release*
Endocannabinoids involved in:

- regulation of **cognitive functions** via neuronal circuits of the cortex
- **Memory** via hippocampal neurons
- **Emotions** via neurons of the amygdala
- **Central processing of pain** via the periaqueductal grey matter, medulla and spinal trigeminal nucleus

Overstimulation of CB1 receptors in the hippocampus and cerebellum, basal ganglia and cortex responsible for many of the cognitive and motor effects of THC

Modulation of the midbrain DA neurons and prefrontal cortical pyramidal cells via THC CB1 stimulation may play role in THC related psychosis.
Endocannabinoid system and brain maturation
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

- Human/animal studies indicate core elements of the dopaminergic system evolve over the adolescent period
  - Synthesis and breakdown enzymes
  - Levels of dopamine and its target receptors
  - Transitory shift in functionality where the ability of DA to modulate interneuron populations emerges
- HPA axis hormones go thru significant changes in the levels and timing of release during adolescence
- Both systems interact with the endocannabinoid system
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)
- Gyrification abnormalities
- Use before 17 yrs: smaller whole brain and percent cortical grey matter
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

Reviewed in Cookey, Bernier, Tibbo Schiz Research 2014
Recent neuroimaging reviews in Psychosis:


- 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)
- Review somewhat inconclusive
- 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.
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
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
Psychosocial Interventions to Reduce Cannabis Use in the Early Psychosis Population.
Aydin C, Tibbo P, Ursuliak Z. Early Intervention in Psychiatry 6(S1)115; 2012

- 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
However:

- 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
Two-Hit Hypothesis for Psychosis

Maynard et al, 2001; Comblatt et al, 2004
Genotype contributions to dopamine metabolism

- COMT encodes a key enzyme that metabolizes dopamine in the frontal cortex\(^1\)

- 2 alleles—valine (Val) and methionine (Met)\(^2\)

- Val allele associated with greater metabolism of dopamine and poorer frontal function\(^1\)

- Some, but not all, family studies show the Val allele confers risk for schizophrenia\(^2\)

COMT=Catechol-O-methyl-transferase.

Schizophreniform symptoms at 26

Schizophreniform symptoms at 26

*noted only in adolescent cannabis use, not adult

* Issues with reproducibility

Halifax/Edmonton Study

- **Exploring the Interplay between COMT and Cannabis Consumption in Psychotic Disorders (Halifax/Edmonton study)**
  (Submitted to Society of Biological Psychiatry Annual meeting (May 2015))

- N=204
- **COMT genotype** was not a significant predictor in this preliminary analysis. Subgroup analysis in schizophrenia spectrum disorders and substance induced psychosis, found borderline significance for the first subgroup (p=0.055) and significance for the second at p=0.046.
- Markers on genes **BDNF and AKT1** are next to be genotyped.
Can we propose a **model** which involves several pathways from cannabis to psychosis?

Factors that are key to the various pathways include

- Early initiation/lifetime use of cannabis versus recent cannabis use.
- Underlying genetic vulnerability to psychosis/schizophrenia.
- Ongoing cannabis use after psychosis onset versus stopping cannabis use.
Early Initiation cannabis use (cumulative)

Disrupted neurodevelopmental processes

High Genetic Vulnerability (e.g. COMT)

Low Genetic Vulnerability

Ongoing use

Poor outcomes

Psychosis

Early AO
Long DUP
N Cognition
Positive sx’s
N brain structure

Cannabis use stops

Good outcome

Subclinical symptoms

Good outcomes

Asymptomatic
Future research with cannabis and psychosis

There is clearly a need for future research to clarify and confirm pathways. The ideal study would include the following methods:

- A first-episode psychosis population with narrow diagnostic definitions.
- A detailed history and description of cannabis use, including: age at initiation; frequency and extent of cannabis consumed; and a clear description of patterns of recent use.
- History of other risk factors for psychosis (e.g., childhood trauma).
- Measures of vulnerability or proneness to schizophrenia and psychosis – these may be indirect (e.g., familial history) or direct (genetics)
- A longitudinal study design with clear baseline and follow-up measures of psychopathology, cognitive functioning, biological measures and ongoing cannabis use.
Other discussion points

- Another variable to consider: potency of cannabis
  - Di Forti et al examined higher potency cannabis
  - Smoking ‘skunk’ leads to an increased risk of developing psychosis

- Also need to consider concentrations of other cannabinoids in cannabis preparations (e.g. cannabidiol)

- Medical marijuana for adolescent populations
  - Crocker, Tibbo *Clinical Pharmacology and Therapeutics* 2015