

How Cannabis in Adolescence Influences Mood and Increases the Risk of Depression and Suicide

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Why I am interested in cannabis

- 2001: Many young patients were presenting severe depression and long-term cannabis consumption (since adolescence)
- 2003: I started studying the relationship between cannabis and depression in my lab
- More than 30 scientific articles published on this topic since then
- Expert witness in the Parliament of Quebec to increase the legal age of cannabis consumption and in the Superior Court of Quebec to regulate the advertisement of cannabis

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Objectives

- What is depression?
- What is suicide?
- Why does cannabis trigger depression and suicide?
- Can you treat your adolescent who consumes cannabis and suffers from depression?

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Jacques, 18 yo, exchange student at McGill.

He was brought to the emergency at the MGH by police who saw him standing too close to the subway for a long time. He was hearing voices asking him to jump.

Suicidal ideations and severe symptoms of depression: insomnia, anxiety, no appetite, pessimism, lack of concentration for the previous 2 months. Psychotic features.

Absence of depression in the past, no mental health issues.

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Born in the South of France, adopted child. Mother is a nurse, father is an accountant.

At 14 yo Jacques started smoking cannabis occasionally (once a month, in a social context). Cannabis helped him to better socialize and made him euphoric ("high") and relaxed.

At 17 yo, he started smoking cannabis every week. At age 18, he moved to Montreal for an international exchange (Faculty of Business) and tried cannabis at high potency (THC 30%), offered by his older room-mates.

His mood became worse and worse, sleeping only 2-3 hours a day, isolation, no friends, no contacts with his family.....

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What is depression?



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Mood Disorders and Depression.

It's not only a state of mind.

The symptoms of depression

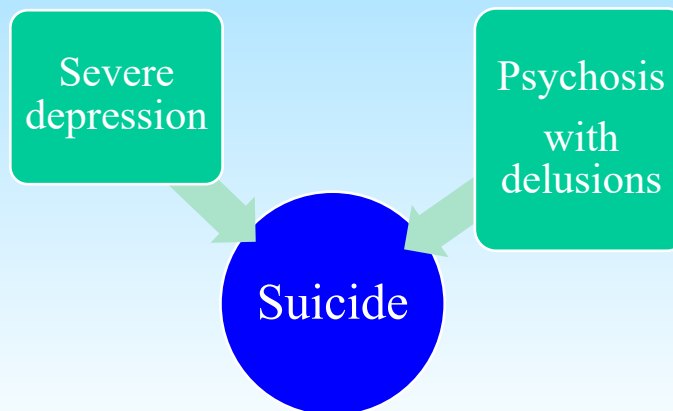
Emotional Symptoms Include:	Physical Symptoms Include:
Sadness	Vague aches and pains
Loss of interest or pleasure	Headache
Overwhelmed	Sleep disturbances
Anxiety, Irritability	Fatigue
Diminished ability to think or concentrate, indecisiveness	Back pain
Excessive or inappropriate guilt	Significant change in appetite resulting in weight loss or gain

SUICIDE

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association. 2000:345-356,489

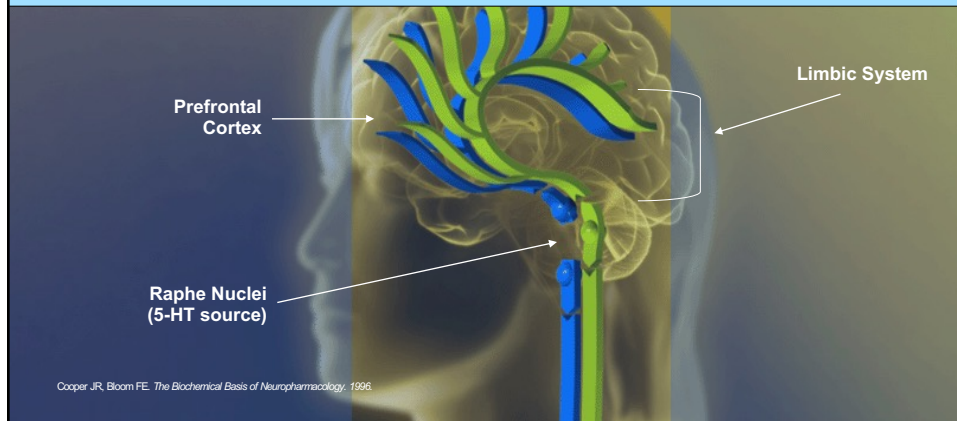
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**Suicide is triggered by a severe depression
and/or or a psychotic episode (delusional voices)**



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Serotonin



Decrease of 5-HT neurotransmission in depression and suicidal behavior

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What is suicidal behavior?



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What is a suicidal behavior?

- **Suicidal thoughts:** Feeling that life is not worth living, feeling that you would be better off dead or that a natural death would be welcome.
- **Plan for suicide:** consulting internet for different options
- **Suicidal attempts**
- **Suicide**

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From depression to Suicide Warning Signs: 1

Know what to look for:



Talk or threats to harm oneself



Looking for a way to kill oneself



Talking or writing about death, dying or suicide

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From depression to Suicide Warning Signs: 2



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Who Is Most Likely to Commit Suicide?

- Suicide rates are highest in **teens**, young adults, and the elderly.
- Suicide risk is also higher in people :
 - who have attempted suicide in the past
 - with **substance abuse** problems: alcohol and cannabis
 - with a family history of suicide
 - with friends or co-workers who have killed themselves (IMITATION FACTOR)
 - who are prone to violent or **impulsive behavior**
 - with a history of physical, emotional, or sexual abuse
 - with long-term pain or a disabling or terminal illness
 - who have recently been released from a psychiatric hospitalization (This often is a very frightening period of transition.)
 - in certain professions, such as police officers and **health care** providers who work with terminally ill patients
 - Older people who have lost a spouse through death or divorce

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Why does cannabis trigger depression and suicide?



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Cannabis pharmacological principles

**Δ -9- Tetrahydrocannabinol
(Δ -9-THC):**
CB1 partial agonist

Cannabidiol (CBD):
5-HT1A partial agonist and TRPV1
agonist



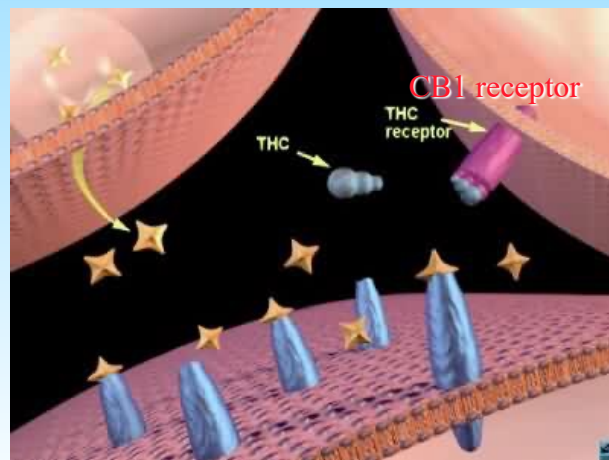
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Cannabis: most popular



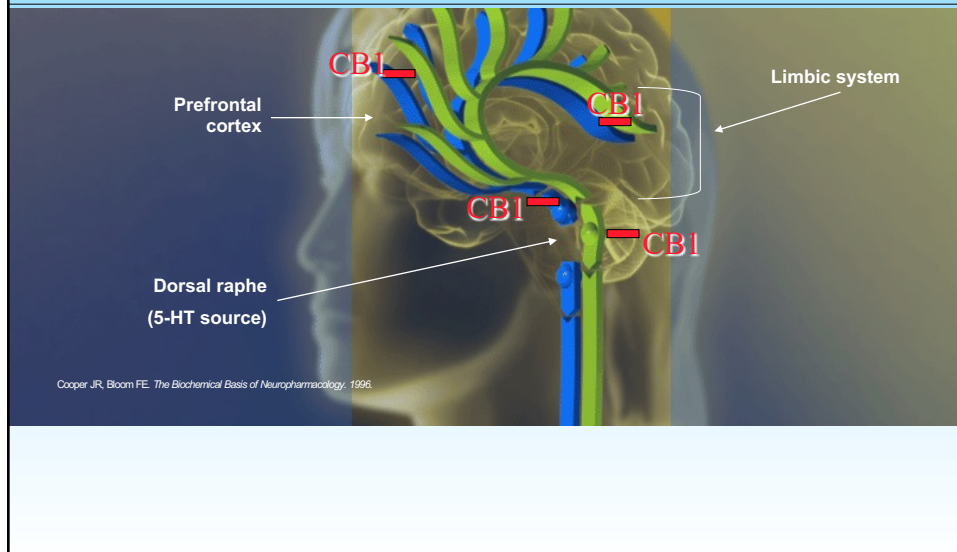
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THC and CB1 receptor



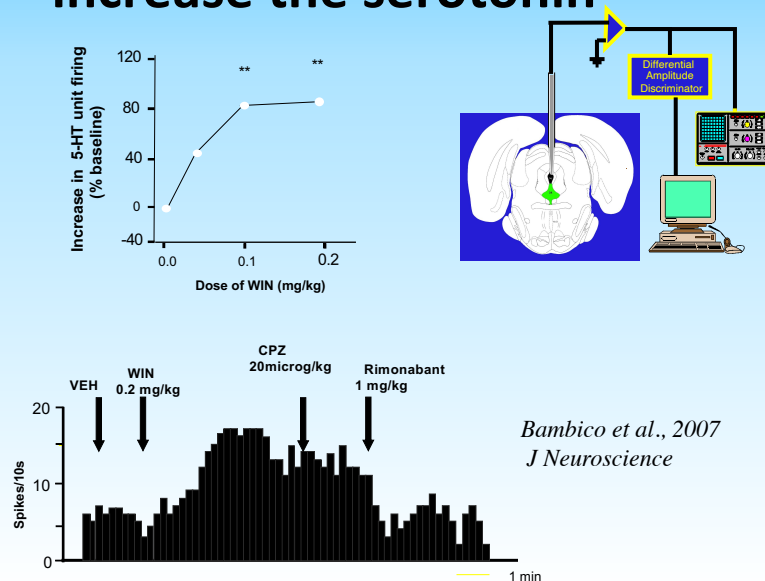
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The CB1 receptors are located in the emotional brain and interact with serotonin



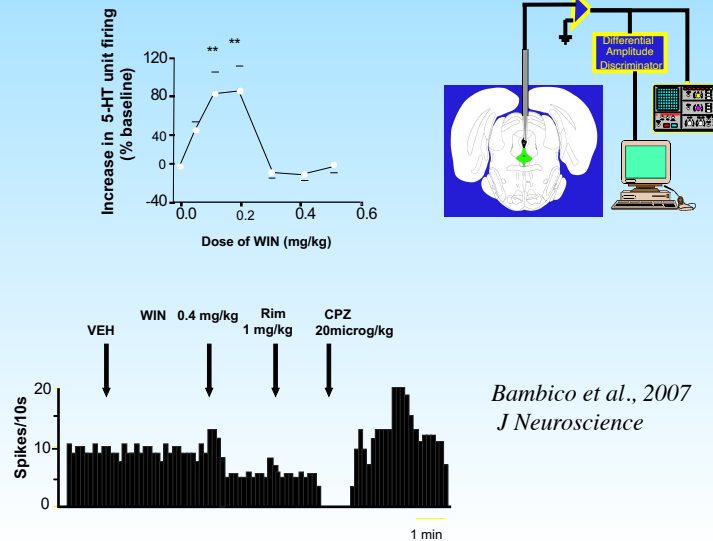
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Cannabinoids at low doses increase the serotonin



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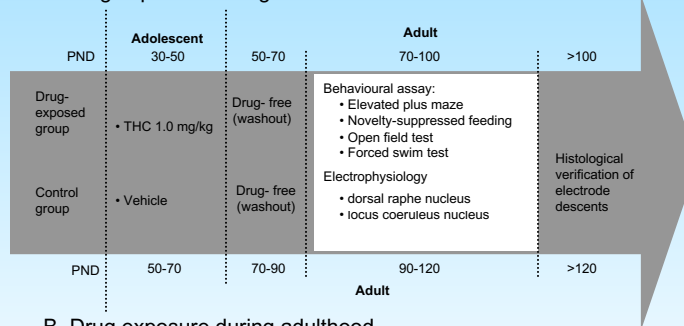
Cannabinoids at high doses decrease serotonin



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Cannabis Adolescence Exposure

A. Drug exposure during adolescence

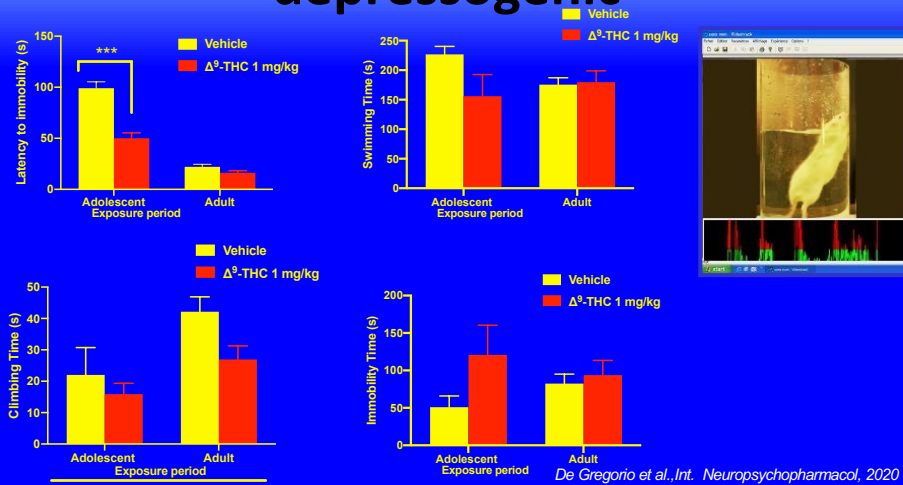


B. Drug exposure during adulthood

Journal of Neuroscience, 2009

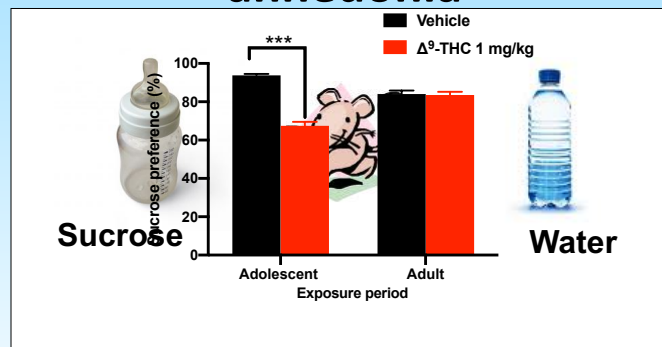
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FST: THC decreases of the latency to immobility = depressogenic



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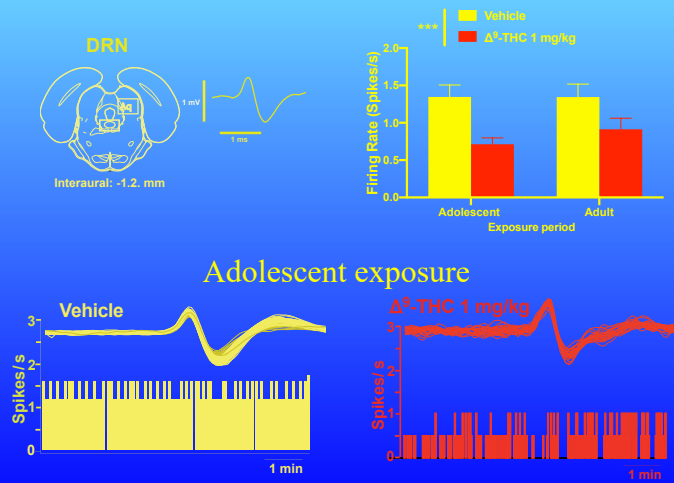
Sucrose test Anhedonia = lack of pleasure Adolescent use of THC increases anhedonia



De Gregorio et al., Int. J. Neuropsychopharmacol 2020

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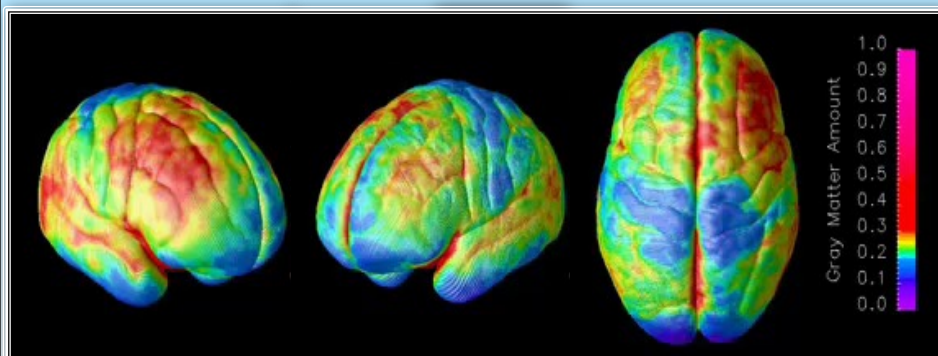
Decreased 5-HT firing activity in rats exposed to THC during adolescence and adulthood



De Gregorio et al., *Int. J. Neuropsychopharmacol*, 2020

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Brain development in healthy youth (Ages 5 – 25)



Copyright © 2004 The National Academy of Sciences, USA
Gogtay, N., Giedd, J.N., et al. (2004)
Dynamic mapping of human cortical development during childhood through early adulthood
Proceedings of the National Academy of Sciences, 101 (21), 8174 – 8179

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More than 30 brain imaging studies in people using cannabis in young age



Long-term marijuana use is associated with decreased gray matter in the bilateral orbitofrontal gyri, as well as greater functional connectivity in the orbitofrontal cortex

Lorenzetti et al., 2016, Biol. Psych.

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Does Adolescent cannabis consumption cause depression ?

Research

JAMA Psychiatry | Original Investigation

Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood A Systematic Review and Meta-analysis

Gabriella Gobbi, MD, PhD; Tobias Atkin, BA; Tomasz Zytynski, MD; Shouao Wang, MSc; Sorayya Askari, PhD; Jill Boruff, MLIS; Mark Ware, MD, MSc; Naomi Marmorstein, PhD; Andrea Cipriani, MD, PhD; Nandini Dendukuri, PhD; Nancy Mayo, PhD

Supplemental content

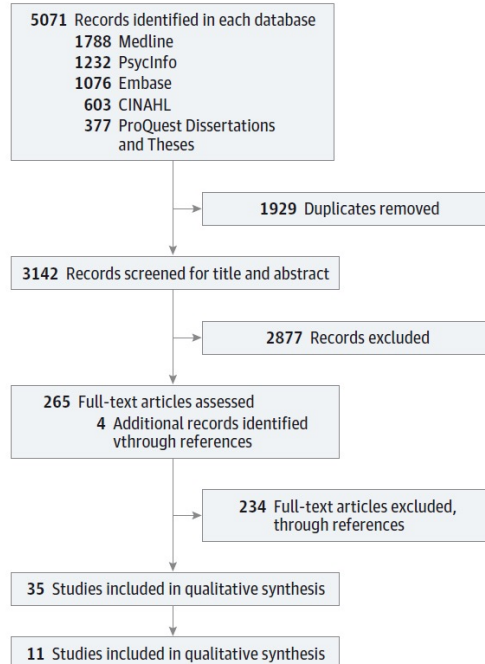
IMPORTANCE Cannabis is the most commonly used drug of abuse by adolescents in the world. While the impact of adolescent cannabis use on the development of psychosis has been investigated in depth, little is known about the impact of cannabis use on mood and suicidality in young adulthood.

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Longitudinal prospective studies Adjusted for premorbid depression, anxiety and other main factors



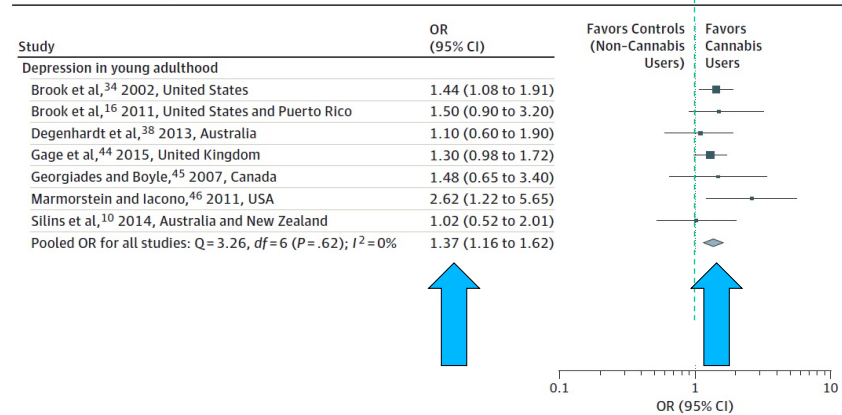
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Cannabis in adolescence increases the risk of depression by 37%

Figure 2. Forest Plot Showing Adjusted Odds Ratio (OR) and 95% CIs for Depression and Anxiety in Young Adulthood According to Cannabis Use in Individual Studies

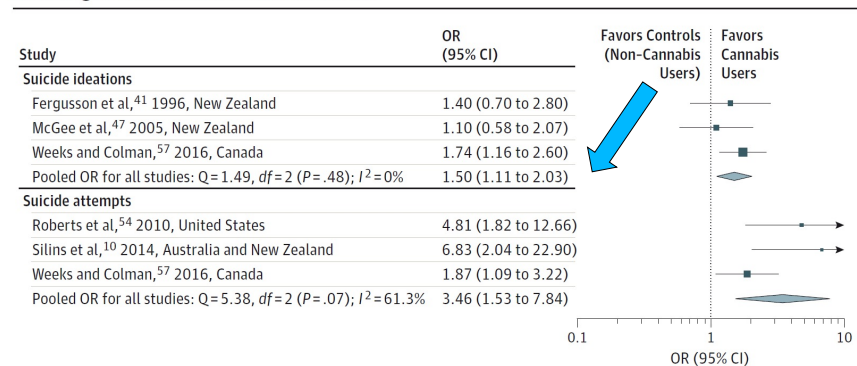


Gobbi et al., JAMA Psych 2019

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Cannabis in adolescence increases the risk of suicidal ideations by 50%

Figure 3. Forest Plot Showing Adjusted Odds Ratio (OR) and 95% CIs for Suicidal Ideations and Attempts According to Cannabis Use in Individual Studies



Gobbi et al., JAMA Psych 2019

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A genetically informed study on the association of cannabis, alcohol, and tobacco smoking with suicide attempt

Massimiliano Orri^{1,2} · Jean R. Séguin^{3,4} · Natalie Castellanos-Ryan^{3,5} · Richard E. Tremblay^{3,6,7} · Sylvana M. Côté^{2,3,8} · Gustavo Turecki¹ · Marie-Claude Geoffroy^{1,9}

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Table 3 Multivariate Mendelian randomization estimates for the association of substance use with suicide attempt.

From: A genetically informed study on the association of cannabis, alcohol, and tobacco smoking with suicide attempt

	Inverse variance weighted		MR-Egger method		
	OR (95% CI)	P	OR (95% CI)	P	P intercept
Cannabis use	1.25 (1.09–1.43)	0.001	1.23 (1.01–1.50)	0.044	0.841
Alcohol use (drinks/week)	0.90 (0.54–1.52)	0.702	1.05 (0.52–2.10)	0.890	0.519
Smoking initiation	0.96 (0.76–1.21)	0.735	0.91 (0.60–1.40)	0.675	0.780

No. of SNPs used in the analysis is 248. *Q* (245 degrees of freedom), 397.9, *P* < 0.001.

“Only cannabis shows a direct pathway to suicide attempt”

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Why are these results important?

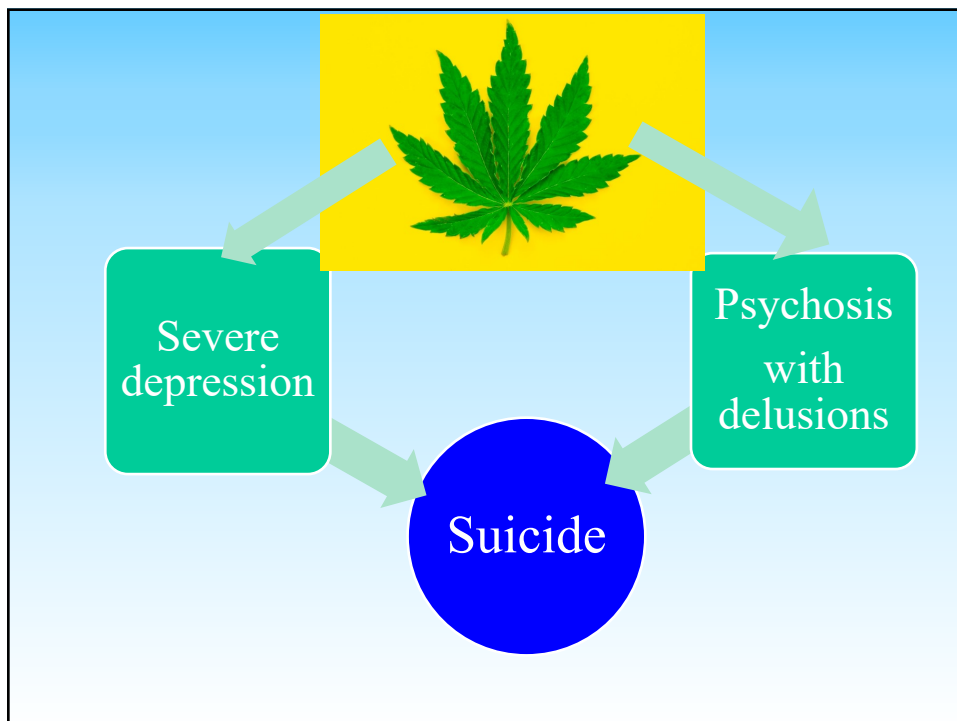
- Controlled for premorbid depressive symptoms or suicidality behaviour (also family history of depression)
- The effect size is modest, but use of cannabis is common (in the US, 20.9% of adolescents report monthly use of cannabis and 7% of high school seniors are daily or near-daily users)
- The *population attributable risk* (i.e. proportion of cases that would not occur in a population if the factor were eliminated) for cannabis and depression is high.
- smoked cannabis.
-

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How much is too much?

- Data suggest that weekly cannabis may have effects on mental health
- Daily consumption of cannabis for many years undoubtedly has effects on mental health
- Cannabis potency: the more concentrated THC is, the more pronounced the effects on mental health are

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What can you do if your child consumes cannabis?




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What can you do if your child consumes?

- Take time to talk with the child
- Find the best moment for him/her, not for you!
- Listen to their emotions
- Ask about the consumption: How much? What kind of cannabis? How often? What concentration level? Where do you buy it?
- Seek medical and/or psychological help

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What doctors can do for depression associated with cannabis consumption

- 1) Motivational therapy
- 2) Cognitive behavioral therapy
- 3) Pharmacology : Use of anti-epileptic drugs: gabapentine, sodium valproate, lithium, lamotrigine, topiramate, bupropion, buspar

Mason BJ et al, Neuropsychopharmacology 2012
Lee DC, Drug Alcohol Depend 2019

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Treatment for depression associated with cannabis consumption

Cannabis use is associated with more depressive symptoms at baseline and treatment resistant depression (*Feingold et al., 2017*)

Depression improves if patients stop cannabis
(*Moitra et al. 2016; Lutatch et al., 2020*)

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Treatment for depression associated with cannabis consumption

- After a few days spent at the ED, Jacques was dismissed and followed as an outpatient.
- He was treated with antidepressants plus antipsychotics and started motivational therapy helping him to stop cannabis
- Cannabis was decreased slowly and gabapentine plus benzo at night were also prescribed for the withdrawal symptoms (nightmares, nocturnal sweating, anxiety)
- Psychotherapy

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Take home message

- **Basic and clinical research confirms the long-term effects of adolescent cannabis consumption on depression, even if in absence of pre-morbid conditions.**
- **Cannabinoid interacts with brain areas involved in the regulation of mood, such as 5-HT and the endocannabinoid system.**
- **Cannabis use disorder (CUD) and associated-depression can be cured and (better!) prevented.**

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Acknowledgement



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