Cannabis and the family physician in the age of legalization

Dr Mark A. Ware MBBS MSc
Associate Professor of Anesthesia and Family Medicine
McGill University

Presenter Disclosure

Relationships with commercial interests:

- Grants/Research Support: CanniMed
- Employee: Chief Medical Officer, Canopy Growth Corporation

Potential for conflict(s) of interest:

- Actively involved in research on cannabinoid and pain.
- Argued for a role for therapeutic considerations for cannabis (Clin Pharm Ther 2009, Task Force 2016)

Mitigation of Potential Bias:

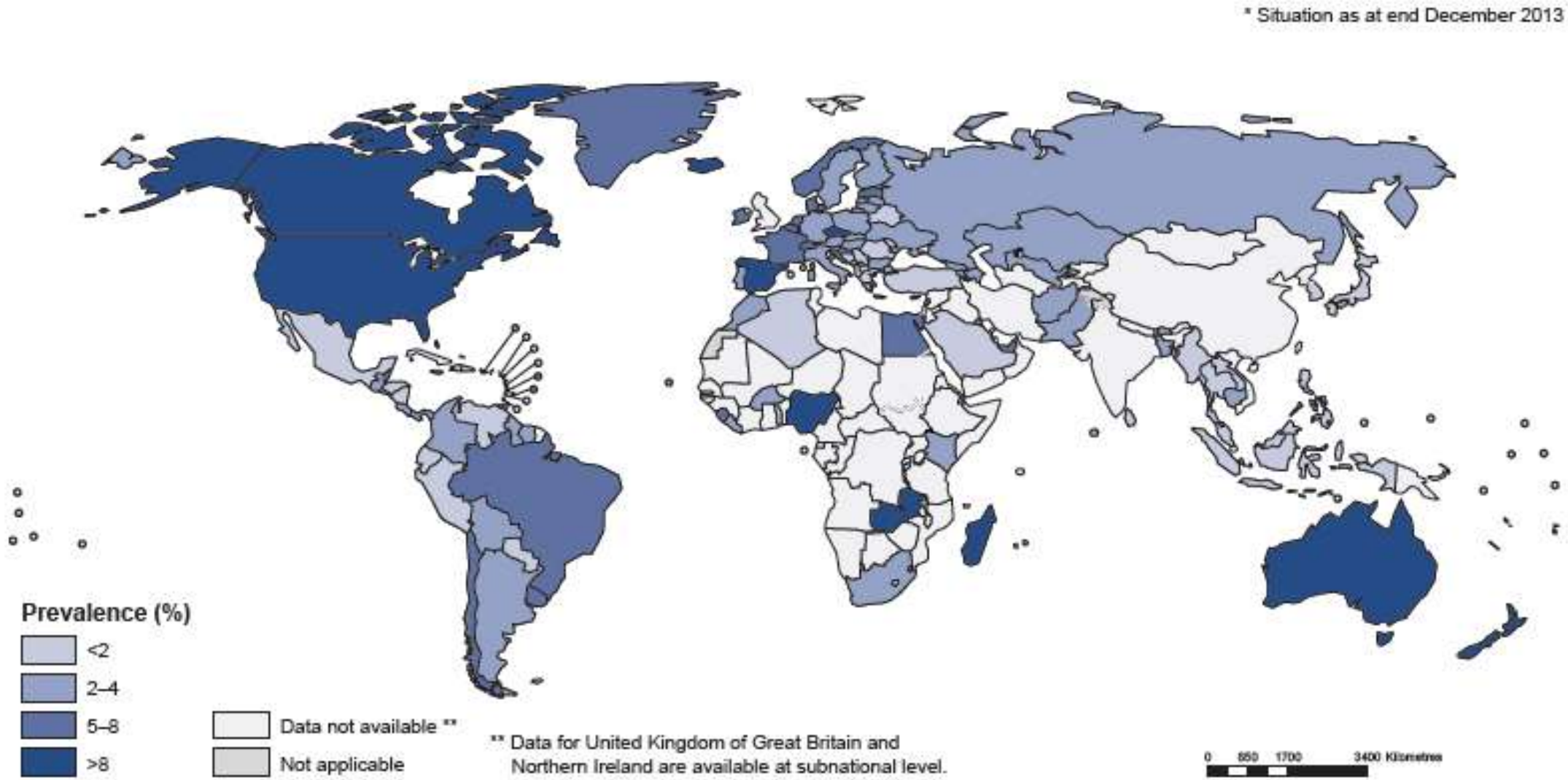
- Attempt at balanced presentation
- No reference to brand names or companies
- Acknowledge perception of therapeutic utility

Presentation Objectives

At the end of this session, the participant will be able to:

1. Appreciate developments in cannabinoid and pain neurobiology
2. Review clinical evidence of safety and efficacy of cannabinoids and pain
3. Consider implications of legal non-medical cannabis on patients and practitioners
4. Buy cannabis at the local store

FIGURE 3.1. ANNUAL PREVALENCE OF CANNABIS USE FOR POPULATION AGED 15–64 YEARS



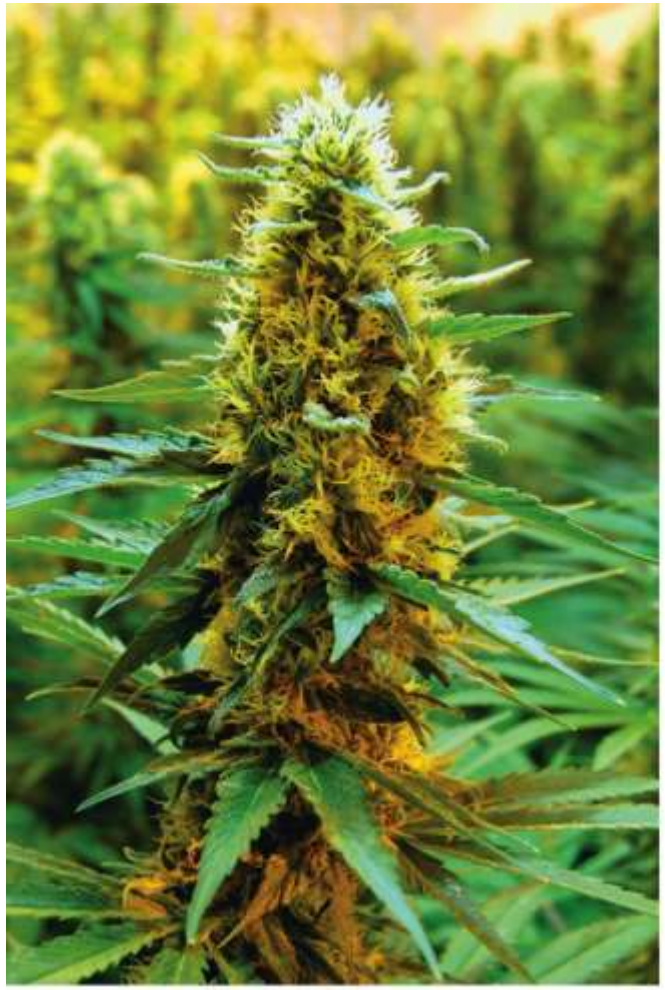
Source: WHO 2016

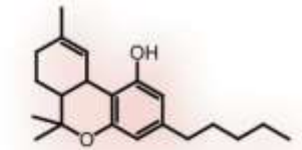
van Bakel *et al. Genome Biology* 2011, **12**:R102
http://genomebiology.com/2011/12/10/R102

Genome Biology

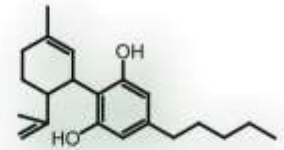
RESEARCH Open Access

The draft genome and transcriptome of *Cannabis sativa*

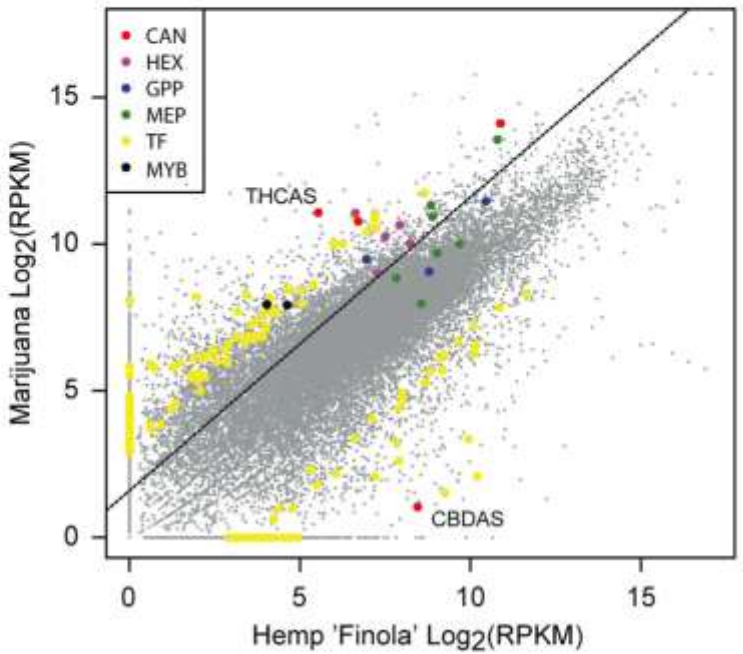




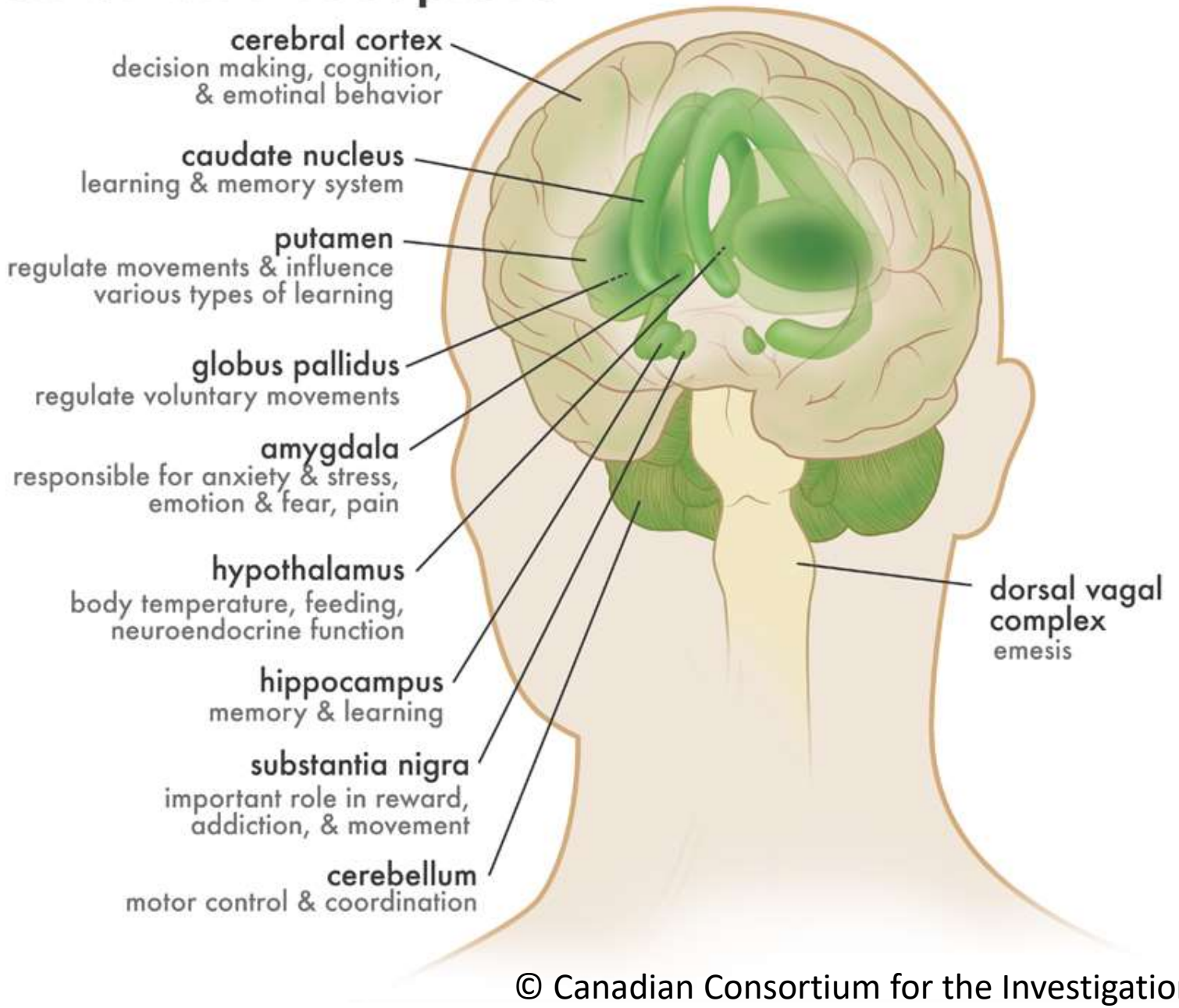
Δ^9-Tetrahydrocannabinol



Cannabidiol



Distribution of CB1 receptors



Synthetic pharmaceutical approaches

- FAAH inhibition
  - Pfizer compound failed in OA knee trial (Huggins 2012)
- Peripherally restricted CB1 agonist
  - AstraZeneca compound status unknown (Yu 2010)
- CB2 agonists
  - GSK compound failed in 3rd molar extraction trial (Ostenfeld 2011)
- CB1 antagonists
  - Rimonabant approved in Europe for obesity and smoking cessation
  - Withdrawn in 2014 for safety concerns (depression and suicidality)

Prescription cannabinoids

Nabilone (0.25 - 1.0mg)

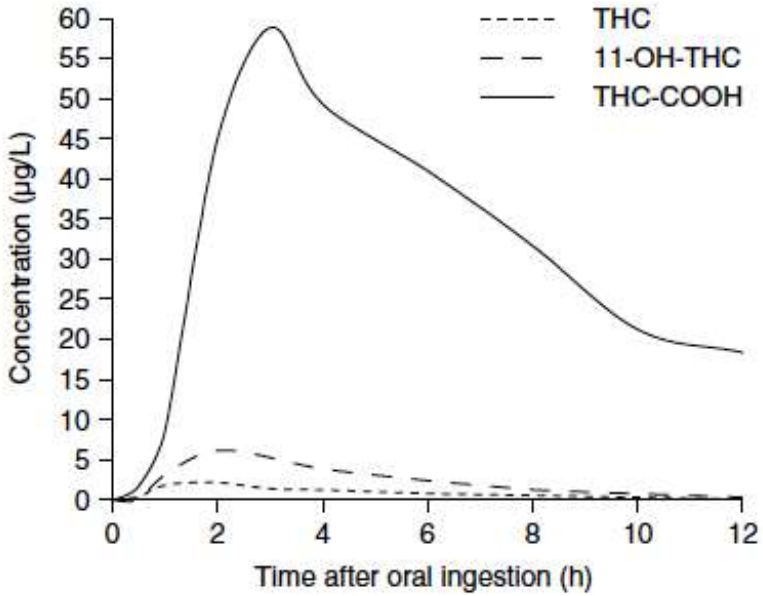
- Oral capsule
- Approved for **chemotherapy-induced nausea and vomiting**

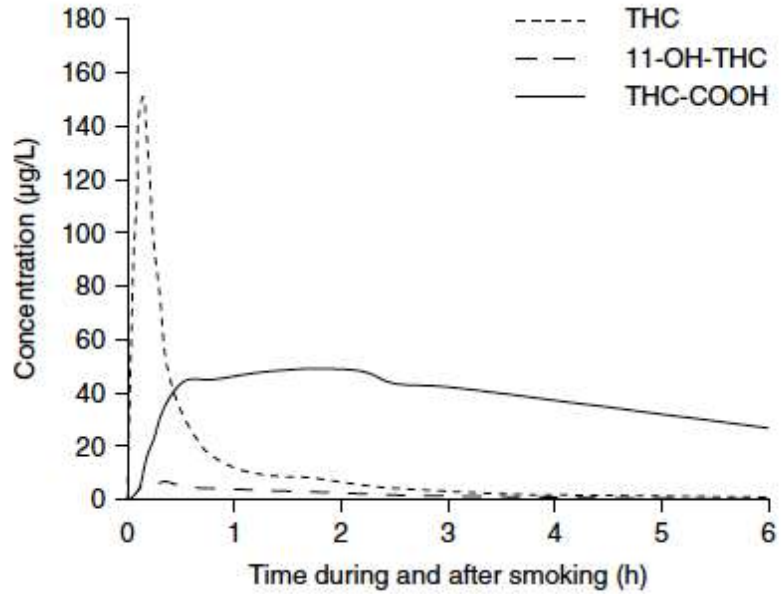
Nabiximols (2.7mg THC + 2.5mg CBD)

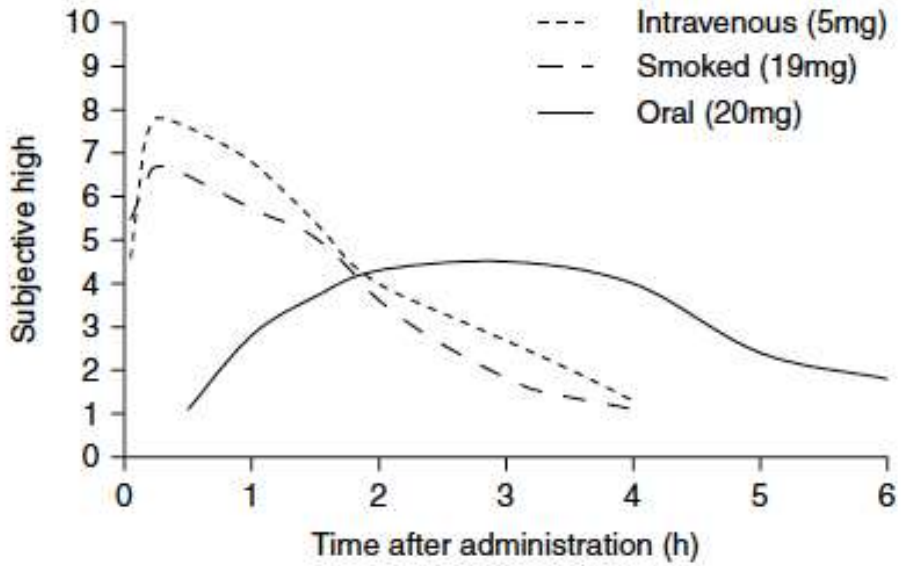
- Oromucosal spray
- Approved in Canada for **multiple sclerosis-associated neuropathic pain, spasticity and advanced cancer pain**

"Medical cannabis may be more accurately defined as the use of cannabis under **ongoing medical supervision**, with an **established diagnosis** of the target symptom-disease complex, **in conjunction** with, or in consideration of, other pharmacological and non-pharmacological approaches, and with the goal of reaching **pre-specified treatment outcomes**"

Clin Pharmacokinet 2003; 42 (4): 327-360
0312-5963/03/0004-0327/$30.00/0







The Evidence Pyramid

Figure 1. Evidence hierarchy: investigations placed in a superior localization in the hierarchy show greater power of evidence[†].

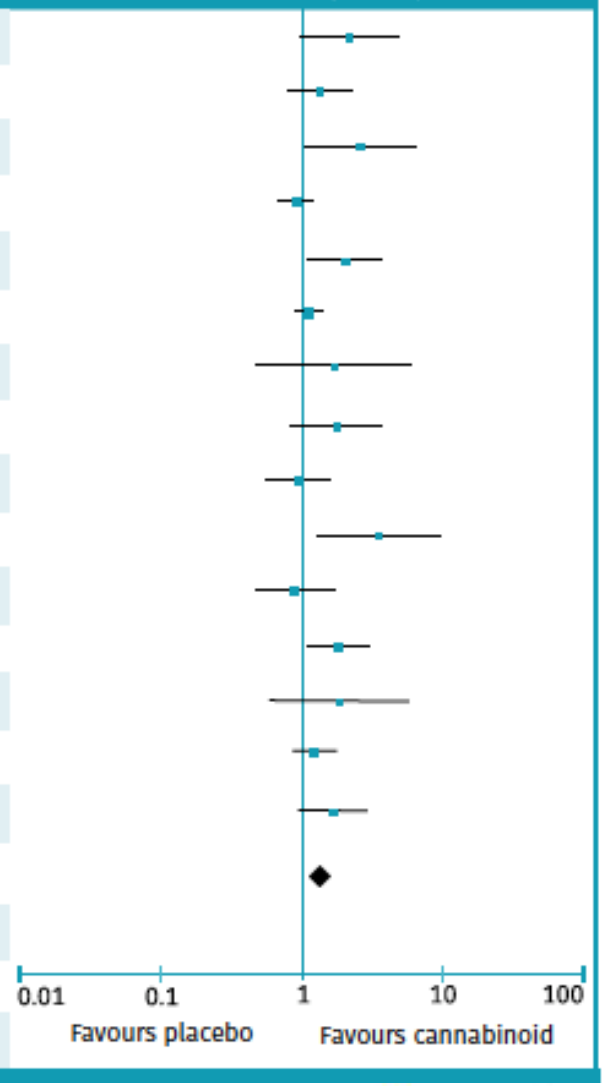
Systematic review of systematic reviews for medical cannabinoids

Pain, nausea and vomiting, spasticity, and harms

G. Michael Allan MD CCFP Caitlin R. Finley MSc Joey Ton PharmD Danielle Perry Jamil Ramji Karyn Crawford MLIS Adrienne J. Lindblad ACPR PharmD Christina Korownyk MD CCFP Michael R. Kolber MD CCFP MSc

Cannabinoids and pain: 30% responder analysis

	EXPERIMENTAL		CONTROL				
STUDY OR SUBGROUP	EVENTS	TOTAL	EVENTS	TOTAL	WEIGHT, %	RISK RATIO* (95% CI)	RISK RATIO* (95% CI)
Abrams, 2007	13	25	6	25	4.2	2.17 (0.98 to 4.79)	
Berman, 2004	34	93	13	48	7.2	1.35 (0.79 to 2.31)	
Ellis, 2009	13	28	5	28	3.5	2.60 (1.07 to 6.32)	
GW Pharmaceuticals, 2005	54	149	59	148	12.7	0.91 (0.68 to 1.22)	
Johnson, 2010	23	53	12	56	6.4	2.03 (1.12 to 3.65)	
Langford, 2013	83	167	77	172	14.5	1.11 (0.89 to 1.39)	
Lynch, 2014	5	18	3	18	1.9	1.67 (0.47 to 5.96)	
Nurmikko, 2007	16	63	9	62	4.7	1.75 (0.84 to 3.66)	
Portenoy, 2012	22	90	24	91	7.9	0.93 (0.56 to 1.53)	
Rog, 2005	15	34	4	32	2.9	3.53 (1.31 to 9.51)	
Selvarajah, 2010	8	15	9	15	5.9	0.89 (0.47 to 1.67)	
Serpell, 2014	34	128	19	128	7.8	1.79 (1.08 to 2.97)	
Ware, 2010	16	64	3	22	2.3	1.83 (0.59 to 5.70)	
Wilsey, 2008	46	69	18	33	11.1	1.22 (0.86 to 1.74)	
Wilsey, 2013	35	73	11	38	7.0	1.66 (0.95 to 2.88)	
Total (95% CI)		**1069**		**916**	**100.0**	**1.37 (1.14 to 1.64)**	
Total events	417		272				
Heterogeneity: $\tau^2 = 0.05$; $\chi^2_{14} = 24.42$ ($P = .04$); $I^2 = 43\%$							
Test for overall effect: $Z = 3.32$ ($P = .0009$)							



Systematic review of systematic reviews for medical cannabinoids

Pain, nausea and vomiting, spasticity, and harms

G. Michael Allan MD CCFP Caitlin R. Finley MSc Joey Ton PharmD Danielle Perry
Jamil Ramji Karyn Crawford MLIS Adrienne J. Lindblad ACPR PharmD
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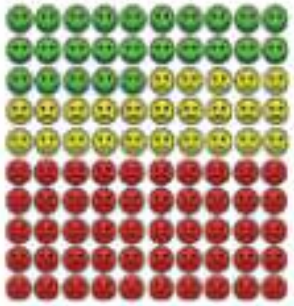
- There is reasonable evidence that cannabinoids improve nausea and vomiting after chemotherapy. They might improve spasticity (primarily in multiple sclerosis).
- There is some uncertainty about whether cannabinoids improve pain, but if they do, it is neuropathic pain and the benefit is likely small.
- Adverse effects are very common, meaning that benefits would need to be considerable to warrant trials of therapy

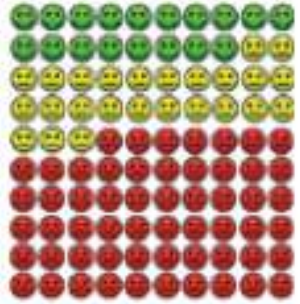
Outcome: Meaningful (approximately 30%) pain improvement
Ordered by decreasing estimated efficacy

Amitriptyline



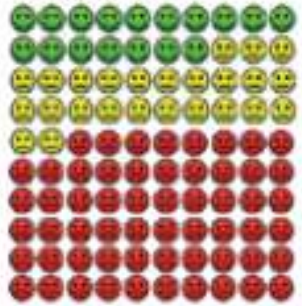
25 Improve with treatment
25 Improve with placebo or no treatment
50 No improvement

High-dose opioids*



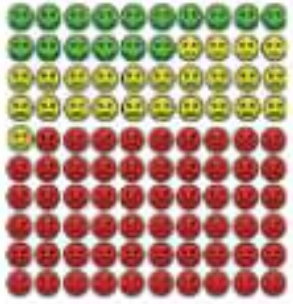
18 Improve with treatment
25 Improve with placebo or no treatment
57 No improvement

Venlafaxine



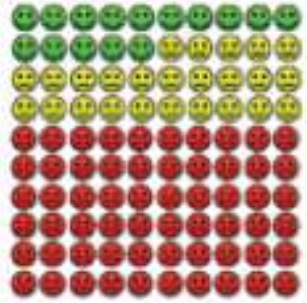
17 Improve with treatment
25 Improve with placebo or no treatment
58 No improvement

Pregabalin



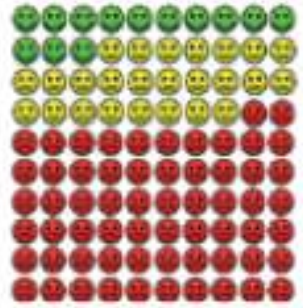
16 Improve with treatment
25 Improve with placebo or no treatment
59 No improvement

Gabapentin



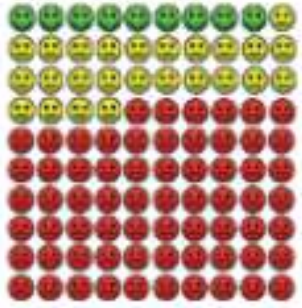
15 Improve with treatment
25 Improve with placebo or no treatment
60 No improvement

Duloxetine



13 Improve with treatment
25 Improve with placebo or no treatment
62 No improvement

Cannabinoids



9 Improve with treatment
25 Improve with placebo or no treatment
66 No improvement

Limitations

- Based on indirect comparisons
- Time frame approximately 4-12 wk
- Details on methods available from **CFPlus**†

Improve with treatment

Improve with placebo or no treatment

No improvement

*60-110 mg of oral morphine per day.

†Go to the full text of the article online and click on the **CFPlus** tab.

Simplified guideline for prescribing medical cannabinoids in primary care

G. Michael Allan MD CCFP Jamil Ramji Danielle Perry Joey Ton PharmD Nathan P. Beahm PharmD
Nicole Crisp RN MN NP-Adult Beverly Dockrill RN Ruth E. Dubin MD PhD FCFP DCAPM Ted Findlay DO CCFP FCFP
Jessica Kirkwood MD CCFP Michael Fleming MD CCFP FCFP Ken Makus MD FRCPC Xiaofu Zhu MD FRCPC
Christina Korownyk MD CCFP Michael R. Kolber MD CCFP MSc James McCormack PharmD Sharon Nickel
Guillermina Noël MDes PhD Adrienne J. Lindblad ACPR PharmD

▸ The guideline suggests that clinicians could consider medical cannabinoids for refractory neuropathic pain and refractory pain in palliative care, chemotherapy-induced nausea and vomiting, and spasticity in multiple sclerosis and spinal cord injury after reasonable trials of standard therapies have failed. If considering medical cannabinoids and criteria are met, the guideline recommends nabilone or nabiximols be tried first. Harms are generally more common than benefits are, and it is important to discuss the benefits and risks of medical cannabinoids with patients for whom they are being considered.

Cochrane Library
Cochrane Database of Systematic Reviews

Cannabis-based medicines for chronic neuropathic pain in adults (Review)

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W

There was no high-quality evidence.

All cannabis-based medicines pooled together were better than placebo for the outcomes substantial and moderate pain relief and global improvement. All cannabis-based medicines pooled together were better than placebo in reducing pain intensity, sleep problems and psychological distress (very low- to moderate-quality evidence).

There was no difference between all cannabis-based medicines pooled together and placebo in improving health-related quality of life, stopping the medication because it was not effective, and in the frequency of serious side effects (low-quality evidence).

More people reported sleepiness, dizziness and mental problems (e.g. confusion) with all cannabis-based medicines pooled together than with placebo (low-quality evidence). There was moderate-quality evidence that more people dropped out due to side effects with cannabis-based medicines than with placebo.

Herbal cannabis was not different from placebo in reducing pain and the number of people who dropped out due to side effects (very low-quality evidence).

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W.
Cannabis-based medicines for chronic neuropathic pain in adults.
Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD012182.
DOI: 10.1002/14651858.CD012182.pub2.

Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

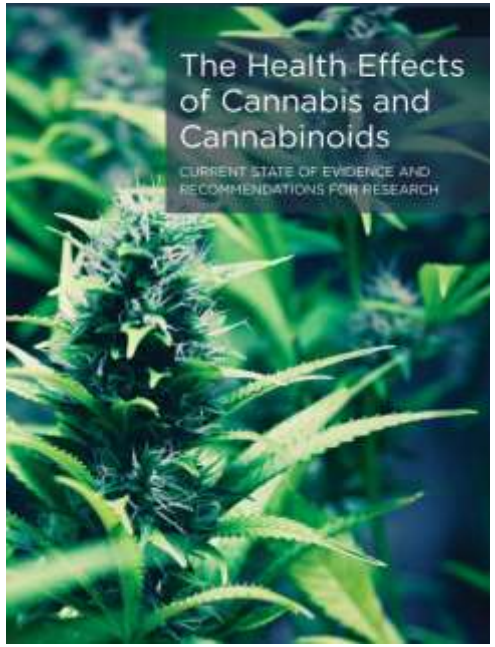
Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

CONCLUSIONS AND RELEVANCE There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As anti-emetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)



Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: Current state of evidence and recommendations for research.* Washington, DC: The National Academies Press.

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

PAIN

Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies

Table 6

Summary of key statistics on the effectiveness of cannabinoids for chronic noncancer pain in randomised controlled trials.

Outcome	Pooled odds ratio (95% CI)	Pooled event rate (%), cannabinoid vs placebo	Number needed to treat to benefit (NNTB) (95% CI)
Pain outcomes			
30% reduction in pain	1.46 (1.16-1.84)	29.0% vs 25.9%	24 (15-61)
50% reduction in pain	1.43 (0.97-2.11)	18.2% vs 14.4%	*
Patient global impression of change			
Perceived "much" to "very much" improved	1.62 (1.34-1.96)	18.9% vs 11.8%	38 (27-62)
	Pooled odds ratio (95% CI)	**Pooled event rate (%), cannabinoid vs placebo**	**Number needed to treat to harm (NNTH) (95% CI)**
Adverse events			
All-cause adverse events	2.33 (1.88-2.89)	81.2% vs 66.2%	6 (5-8)
Study withdrawals—adverse events	3.47 (2.64-4.56)	15.8% vs 4.6%	40 (35-49)

Bold font indicates a statistically significant result. Only categorical outcomes with a moderate or higher GRADE rating are reported here.

* Number needed to treat to benefit unable to be calculated as the pooled odds ratio crossed the line of no effect.

CI, confidence interval.

Commentary

PAIN®

Systematic reviews with meta-analysis on cannabis-based medicines for chronic pain: a methodological and political minefield

Winfried Häuser[a], Nanna B. Finnerup[b,c], R. Andrew Moore[d]

- Low methodological quality studies
- Small trials (n<50); usually positive
- Short trials limit long term efficacy assessment
- Heterogeneity of “chronic pain”
- “Lumping” together all cannabinoids/cannabis based medicines
- Publication bias (unpublished negative trials)
- Safety assessments poor

Neuropsychopharmacology (2017), 1–14

www.neuropsychopharmacology.org

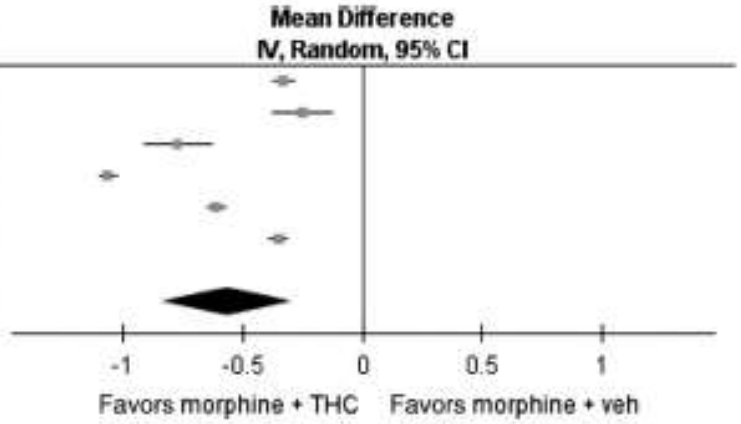
Review Article

Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis

Suzanne Nielsen[*,1,2], Pamela Sabioni[3], Jose M Trigo[3], Mark A Ware[4], Brigid D Betz-Stablein[5], Bridin Murnion[6,7], Nicholas Lintzeris[2,6], Kok Eng Khor[8], Michael Farrell[1], Andrew Smith[9] and Bernard Le Foll[3]

Study or Subgroup	Morphine + THC Mean	SD	Total	Morphine + Vehicle Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cichewicz 1999	1.12	0.09	30	1.45	0.08	30	16.9%	-0.33 [-0.37, -0.29]
Cichewicz 2003	1.13	0.18	12	1.38	0.18	30	16.4%	-0.25 [-0.37, -0.13]
Cox 2007	-0.39	0.17	7	0.38	0.17	28	16.2%	-0.77 [-0.91, -0.63]
Smith 1998	0.44	0.07	30	1.5	0.08	30	16.9%	-1.06 [-1.10, -1.02]
Welch 1992	-0.82	0.07	96	-0.21	0.19	120	16.9%	-0.61 [-0.65, -0.57]
Williams 2008	0.39	0.07	24	0.74	0.06	24	16.9%	-0.35 [-0.39, -0.31]
Total (95% CI)			**199**			**262**	**100.0%**	**-0.56 [-0.83, -0.29]**

Heterogeneity: Tau² = 0.11; Chi² = 926.85, df = 5 (P < 0.00001); I² = 99%
Test for overall effect: Z = 4.10 (P < 0.0001)



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

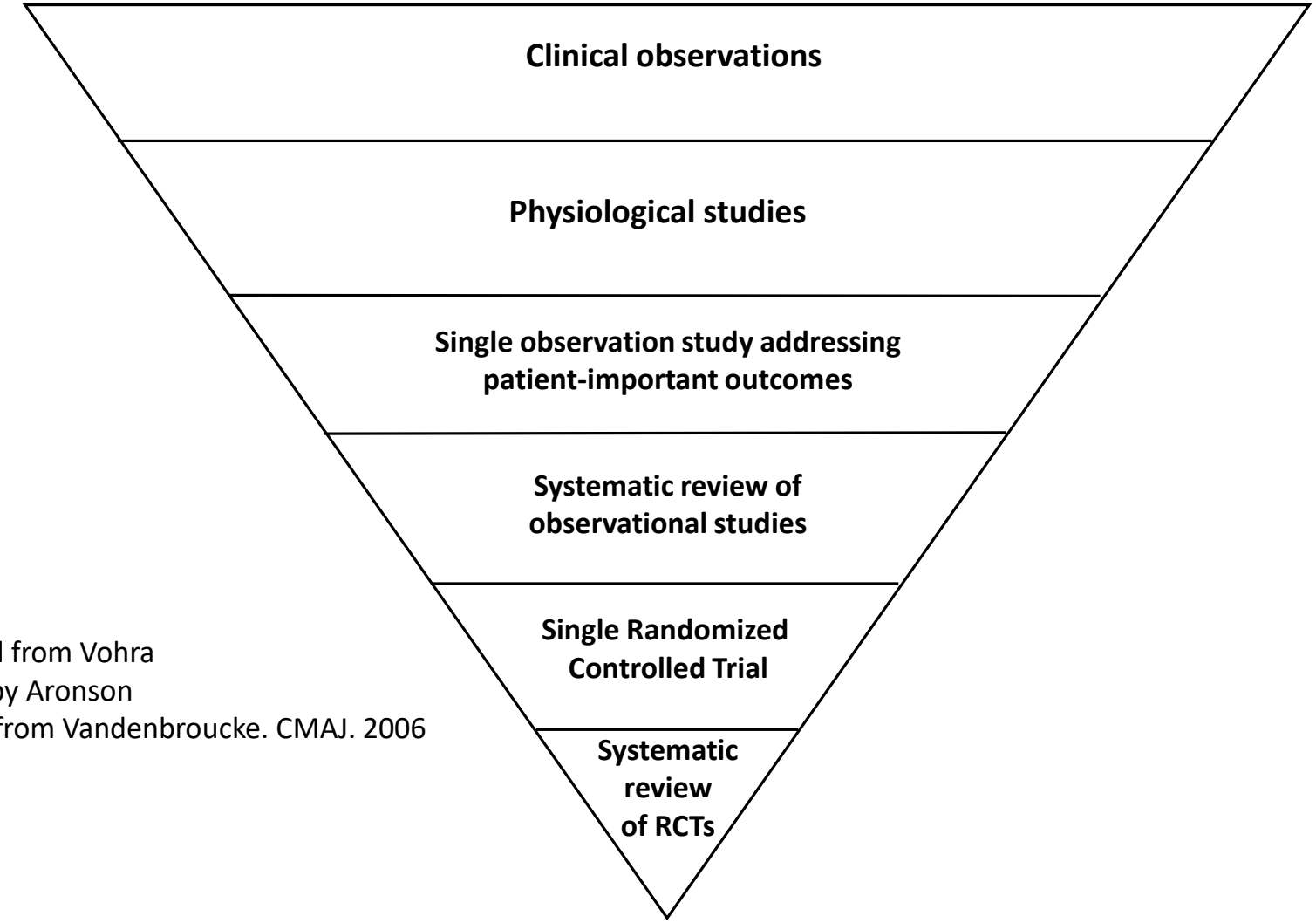
Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

Articles

Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial

*Elizabeth A Thiele, Eric D Marsh, Jacqueline A French, Maria Mazurkiewicz-Beldzinska, Selim R Benbadis, Charuta Joshi, Paul D Lyons, Adam Taylor, Claire Roberts, Kenneth Sommerville, on behalf of the GWPCARE4 Study Group**

The safety pyramid



Borrowed from Vohra
Inspired by Aronson
Adapted from Vandenbroucke. CMAJ. 2006

Safety concerns

- Brain development
- Psychosis
- Cannabis use disorder
- Cognitive function
- Driving
- Drug interactions
- Anxiety/depression
- Cardiovascular effects
- Pregnancy/lactation
- Bronchitis
- Cannabinoid hyperemesis syndrome
- …

Drug harms in the UK: a multicriteria decision analysis

David J Nutt, Leslie A King, Lawrence D Phillips, on behalf of the Independent Scientific Committee on Drugs

www.thelancet.com Vol 376 November 6, 2010

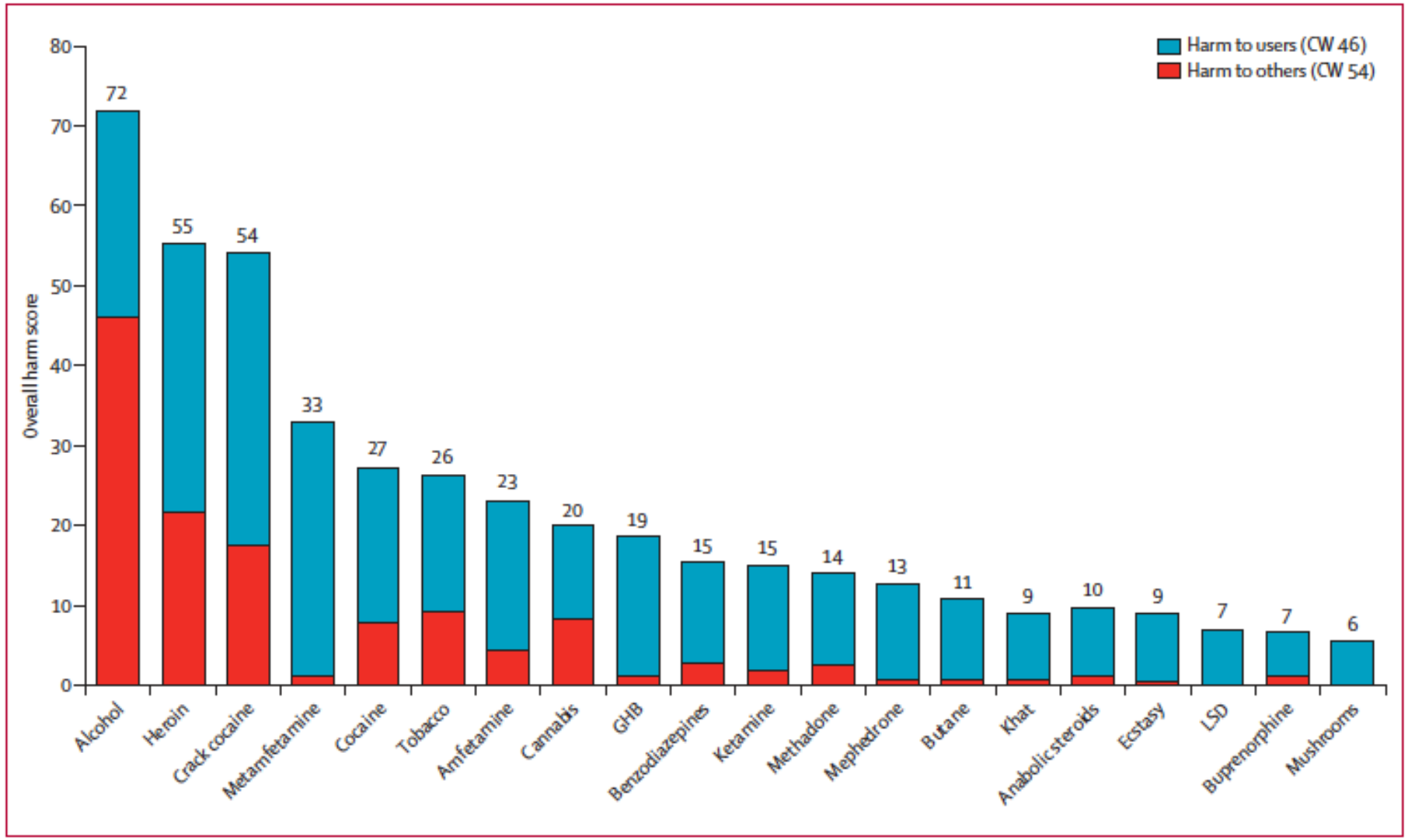


Figure 2: **Drugs ordered by their overall harm scores, showing the separate contributions to the overall scores of harms to users and harm to others**

Uncertainty in understanding cannabis

Science News *from research organizations*

AJPH RESEARCH

Cumulative Lifetime Marijuana Use and Incident Cardiovascular Disease in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

Jared P. Reis, PhD, Reto Auer, MD, MAS, Michael P. Bancks, PhD, MPH, David C. Goff Jr, MD, PhD, Cora E. Lewis, MD, MSPH, Mark J. Pletcher, MD, MPH, Jamal S. Rana, MD, PhD, James M. Shikany, DrPH, and Stephen Sidney, MD, MPH

Conclusions. Neither cumulative lifetime nor recent use of marijuana is associated with the incidence of CVD in middle age. (*Am J Public Health*. 2017;107:601–606. doi:10.2105/AJPH.2017.303654)

JAMA Psychiatry | Original Investigation

Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults

A Systematic Review and Meta-analysis

J. Cobb Scott, PhD; Samantha T. Slomiak, MD; Jason D. Jones, PhD; Adon F. G. Rosen, BS; Tyler M. Moore, PhD; Ruben C. Gur, PhD

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2018.0335
Published online April 18, 2018.

CONCLUSIONS AND RELEVANCE Associations between cannabis use and cognitive functioning in cross-sectional studies of adolescents and young adults are small and may be of questionable clinical importance for most individuals. Furthermore, abstinence of longer than 72 hours diminishes cognitive deficits associated with cannabis use. Although other outcomes (eg, psychosis) were not examined in the included studies, results indicate that previous studies of cannabis in youth may have overstated the magnitude and persistence of cognitive deficits associated with use. Reported deficits may reflect residual effects from acute use or withdrawal. Future studies should examine individual differences in susceptibility to cannabis-associated cognitive dysfunction.

Doctors' group wants to scrap Canada's medical cannabis program

CBC Radio · April 30

Sample Medical Document for the Access to Cannabis for Medical Purposes Regulations

This document may be completed by the applicant's health care practitioner as defined in the Access to Cannabis for Medical Purposes Regulations (ACMPR). A health care practitioner includes medical practitioners and nurse practitioners. In order to be eligible to provide a medical document, the health care practitioner must have the applicant for the medical document under their professional treatment. Regardless of whether or not this form is used, the medical document must contain all of the required information, (see in particular s. 8 of the ACMPR).

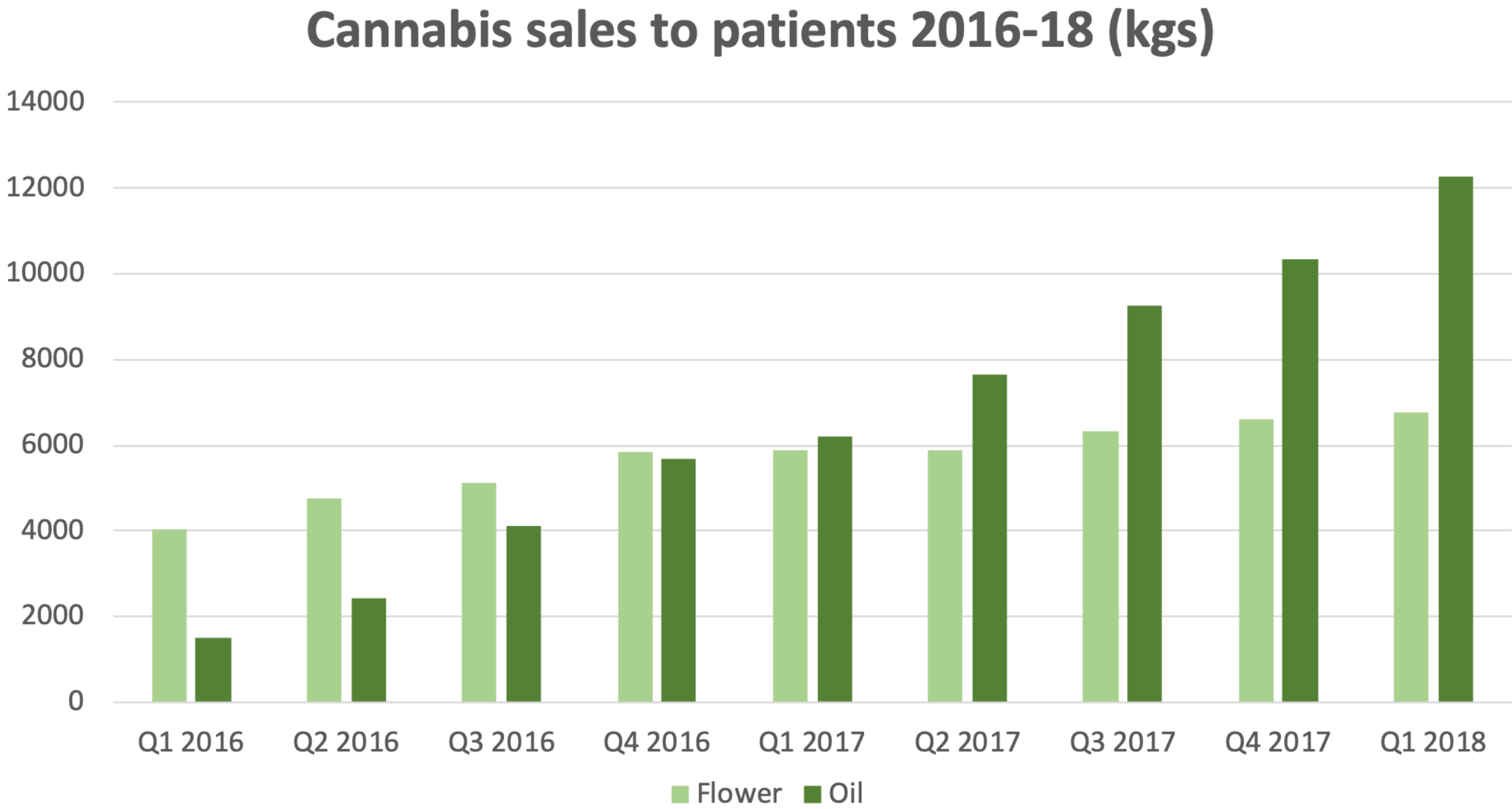
Patient's Given Name and Surname _____

Patient's Date of Birth (DD/MM/YYYY) _____

Daily quantity of dried marihuana to be used by the patient: _____ g/day

The period of use is _____ day(s) _____ week(s) _____ month(s).

NOTE: The period of use cannot exceed one year



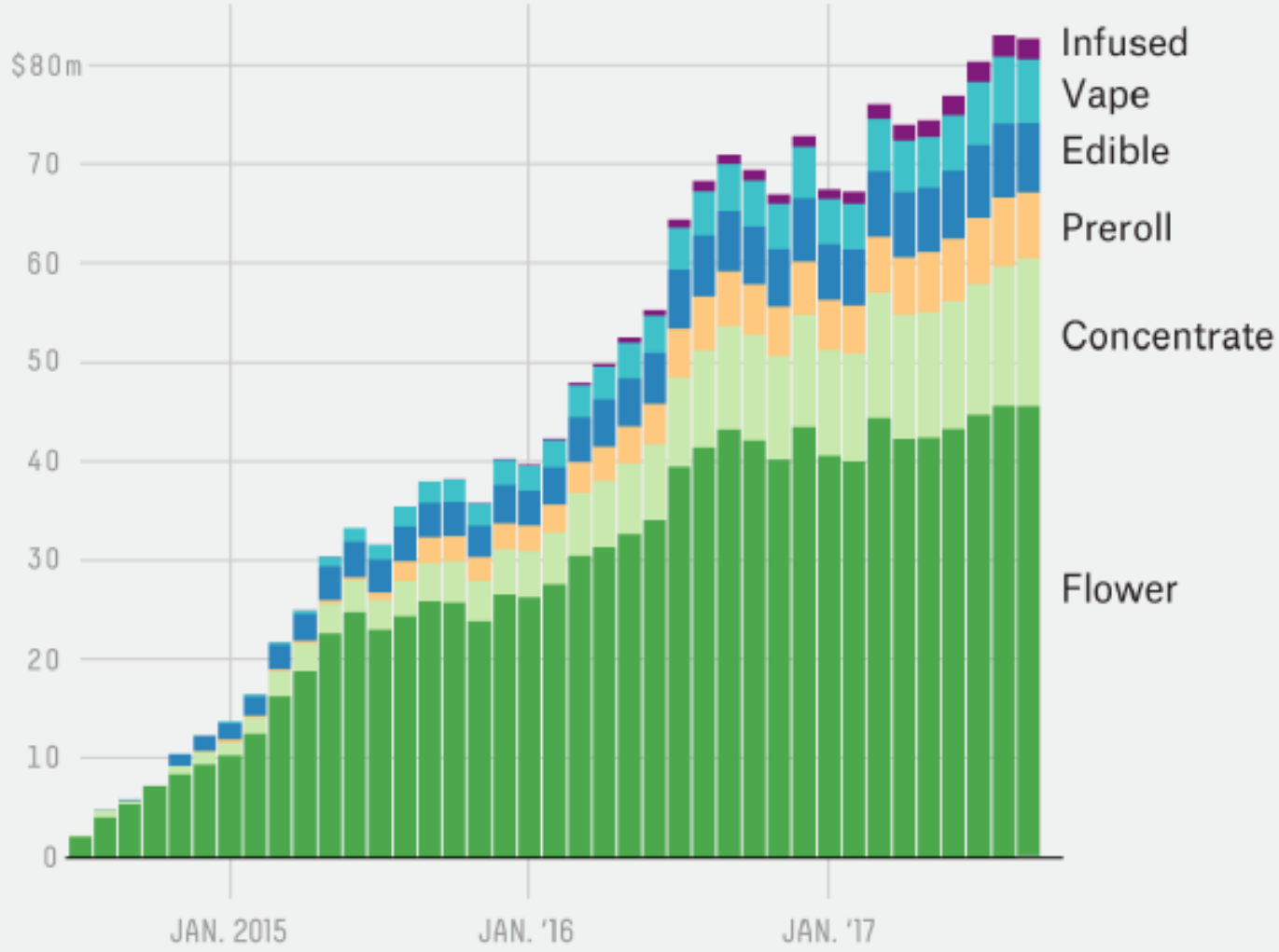
https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-use-marijuana/licensed-producers/market-data.html

Precautions and contraindications

- Contraindications:
  - psychosis
  - unstable heart disease
  - pregnancy
- Precautions
  - screen for cannabis use disorder

It's not just 'bud' anymore

Monthly pre-tax retail sales in Washington state by product type, July 2014 to September 2017



Topical weed products make up a small portion of sales as well.

FiveThirtyEight

SOURCE: TOPSHELFDATA.COM

cmajOPEN

Cannabis use and
recreational users:

Tatiana Ogourtsova PhD OT(c)
Nicol Korner-Bitensky PhD OT

Table 2: Correlation between UFOV driving-related performance and perceived driving ability and safety (n = 45)

Timing and perception	VAS measure; correlation coefficent	
	UFOV-2	UFOV-3
No cannabis use		
Perceived driving ability	$r = 0.13$, $p = 0.4$	$r = 0.18$, $p = 0.2$
Perceived driving safety	$r = 0.06$, $p = 0.7$	$r = 0.18$, $p = 0.2$
At 1 h after cannabis use		
Perceived driving ability	$r = –0.12$, $p = 0.4$	$r = –0.09$, $p = 0.5$
Perceived driving safety	$r = –0.11$, $p = 0.4$	$r = –0.12$, $p = 0.4$
At 3 h after cannabis use		
Perceived driving ability	$r = 0.08$, $p = 0.6$	$r = –0.006$, $p > 0.9$
Perceived driving safety	$r = 0.11$, $p = 0.5$	$r = 0.02$, $p = 0.8$
At 5 h after cannabis use		
Perceived driving ability	$r = –0.40$, $p = 0.006$	$r = –0.005$, $p > 0.9$
Perceived driving safety	$r = –0.38$, $p = 0.009$	$r = –0.05$, $p = 0.7$

Note: r = Pearson correlation coefficient, UFOV = useful field of view, UFOV-2 = complex divided-attention task, UFOV-3 = complex selective-attention task with distractions, VAS = visual analogue scale.

Rapid synthesis: Examining the impact of decriminalizing or legalizing cannabis for recreational use

Waddell K, Wilson MG. Hamilton, Canada: McMaster Health Forum/Michael G. DeGroote Centre for Medicinal Cannabis Research, 31 July 2017.

- 43 documents including five systematic reviews, six non-systematic literature reviews, one program evaluation, and 31 primary studies
- Authors found a **reduction in the perception of risk** of epidemiological harms, and an **increase in the adult use of cannabis**.
- Mixed effects were found with regards to the impact of cannabis on using other substances, with findings indicating a **substitutive or additive effect for the use of alcohol**, largely depending on the construction of the cannabis legislation.
- **Reduction in mortality from opioid overdoses** among states in the U.S. that have legalized medicinal cannabis,
- **Reduction in the rates of suicide** following legalization of medicinal cannabis.
- **Increased cannabis-induced visits to the emergency room**
- **Greater number of telephone calls to poison control centres** following children's accidental ingestion of cannabis

Canada's Lower-Risk Cannabis Use Guidelines (LRCUG)

FAST FACTS

- Canada has among the highest cannabis use rates in the world.
- Fatal and non-fatal injuries from motor-vehicle accidents, as well as dependence and other mental health problems, are the most common cannabis-related harms negatively impacting public health.
- About 1 in 5 people seeking substance use treatment have cannabis-related problems.

negatively impacting public health.
- About 1 in 5 people seeking substance use treatment have cannabis-related problems.

Abstinence

As with any risky behaviour, the safest way to reduce risks is to avoid the behaviour altogether. The same is true for cannabis use.

- **Recommendation 1**
  The most effective way to avoid any risks of cannabis use is to abstain from use. Those who decide to use need to recognize that they incur risks of a variety of – acute and/or long-term – adverse health and social outcomes. These risks will vary in their likelihood and severity with user characteristics, use patterns and product qualities, and so may not be the same from user to user or use episode to another.

Age of initial use

- **Recommendation 2**

  Early initiation of cannabis use (i.e., most clearly that which begins before age 16) is associated with multiple subsequent adverse health and social effects in young adult life. These effects are particularly pronounced in early-onset users who also engage in intensive/frequent use. This may be in part because frequent cannabis use affects the developing brain. Prevention messages should emphasize that, the later cannabis use is initiated, the lower the risks will be for adverse effects on the user's general health and welfare throughout later life.

Choice of cannabis products

- **Recommendation 3**
  High THC-content products are generally associated with higher risks for various (acute and chronic) mental and behavioural problem outcomes. Users should know the nature and composition of the cannabis products that they use, and ideally use cannabis products with low THC content. Given the evidence of CBD's attenuating effects on some THC-related outcomes, it is advisable to use cannabis containing high CBD:THC ratios.

Choice of cannabis products

- **Recommendation 4**
  Recent reviews on synthetic cannabinoids indicate markedly more acute and severe adverse health effects from the use of these products (including instances of death). The use of these products should be avoided.

Cannabis use methods and practices

- **Recommendation 5**
  Regular inhalation of combusted cannabis adversely affects respiratory health outcomes. While alternative delivery methods come with their own risks, it is generally preferable to avoid routes of administration that involve smoking combusted cannabis material, e.g., by using vaporizers or edibles. Use of edibles eliminates respiratory risks, but the delayed onset of psychoactive effect may result in the use of larger than intended doses and subsequently increased (mainly acute, e.g., from impairment) adverse effects.

Cannabis use methods and practices

- **Recommendation 6**
  Users should avoid practices such as "deep-inhalation," breath-holding, or the Valsalva maneuver to increase psychoactive ingredient absorption when smoking cannabis, as these practices disproportionately increase the intake of toxic material into the pulmonary system.

Frequency and intensity of use

- **Recommendation 7**
  Frequent or intensive (e.g., daily or near-daily) cannabis use is strongly associated with higher risks of experiencing adverse health and social outcomes related to cannabis use. Users should be aware and vigilant to keep their own cannabis use—and that of friends, peers or fellow users—occasional (e.g., use only on one day/week, weekend use only, etc.) at most.

Cannabis use and driving

- **Recommendation 8**
  Driving while impaired from cannabis is associated with an increased risk of involvement in motor-vehicle accidents. It is recommended that users categorically refrain from driving (or operating other machinery or mobility devices) for at least 6 hours after using cannabis. This wait time may need to be longer, depending on the user and the properties of the specific cannabis product used. Besides these behavioural recommendations, users are bound by locally applicable legal limits concerning cannabis impairment and driving. The use of both cannabis and alcohol results in multiply increased impairment and risks for driving, and categorically should be avoided.

Special-risk populations

- **Recommendation 9**
  There are some populations at probable higher risk for cannabis-related adverse effects who should refrain from using cannabis. These include: individuals with predisposition for, or a first-degree family history of, psychosis and substance use disorders, as well as pregnant women (primarily to avoid adverse effects on the fetus or newborn). These recommendations, in part, are based on precautionary principles.

Combining risks or risk behaviours

- **Recommendation 10**
  While data are sparse, it is likely that the combination of some of the risk behaviours listed above will magnify the risk of adverse outcomes from cannabis use. For example, early-on-set use involving frequent use of high-potency cannabis is likely to disproportionately increase the risks of experiencing acute and/or chronic problems. Preventing these combined high-risk patterns of use should be avoided by the user and a policy focus.