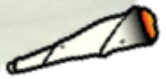
THE PINEAPPLE EXPRESS IS DRIVING MISS DAISY TO USE CANNABIS

MEDS Conference

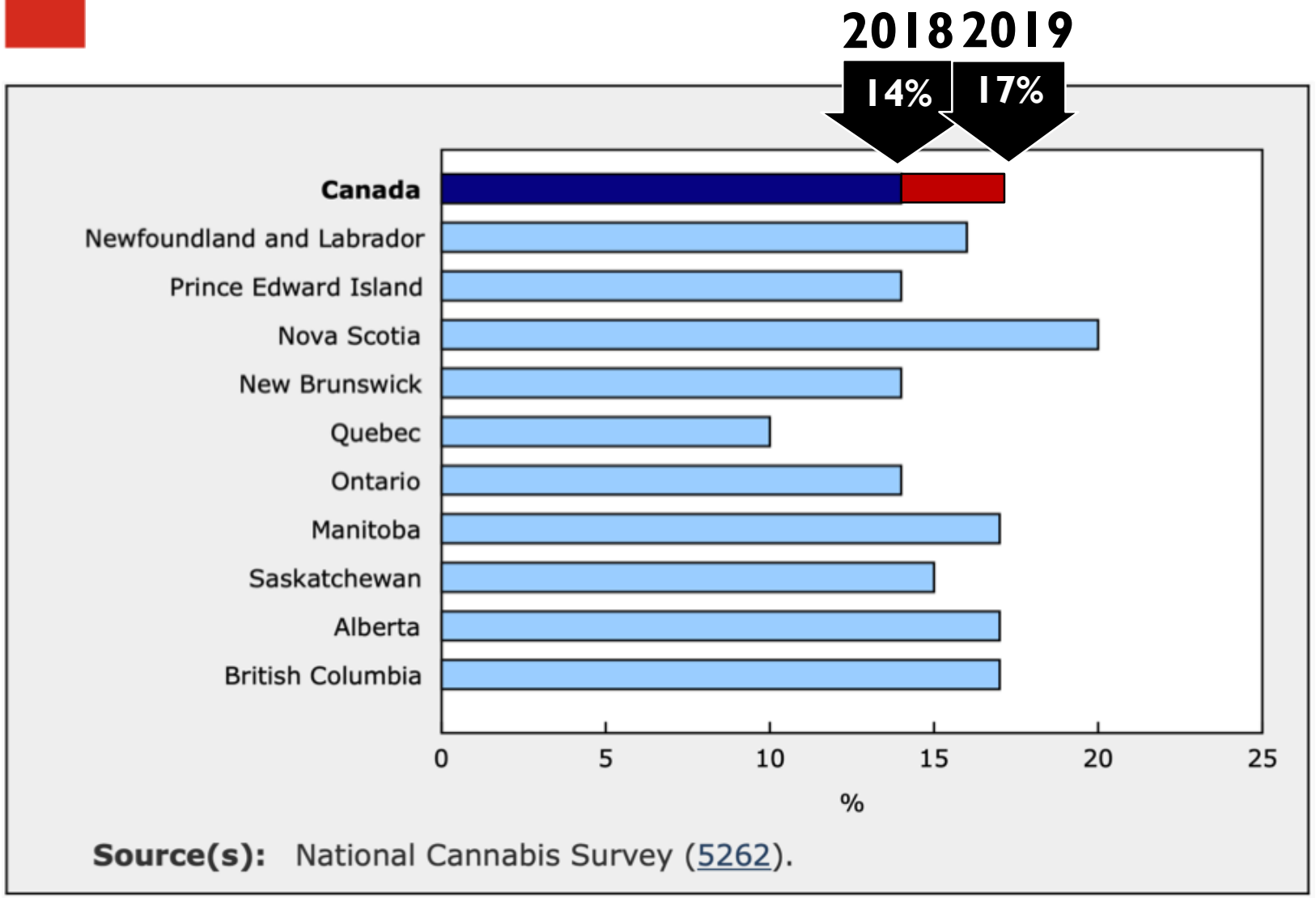
Feb 8, 2020

Jamie Falk, BScPharm, PharmD



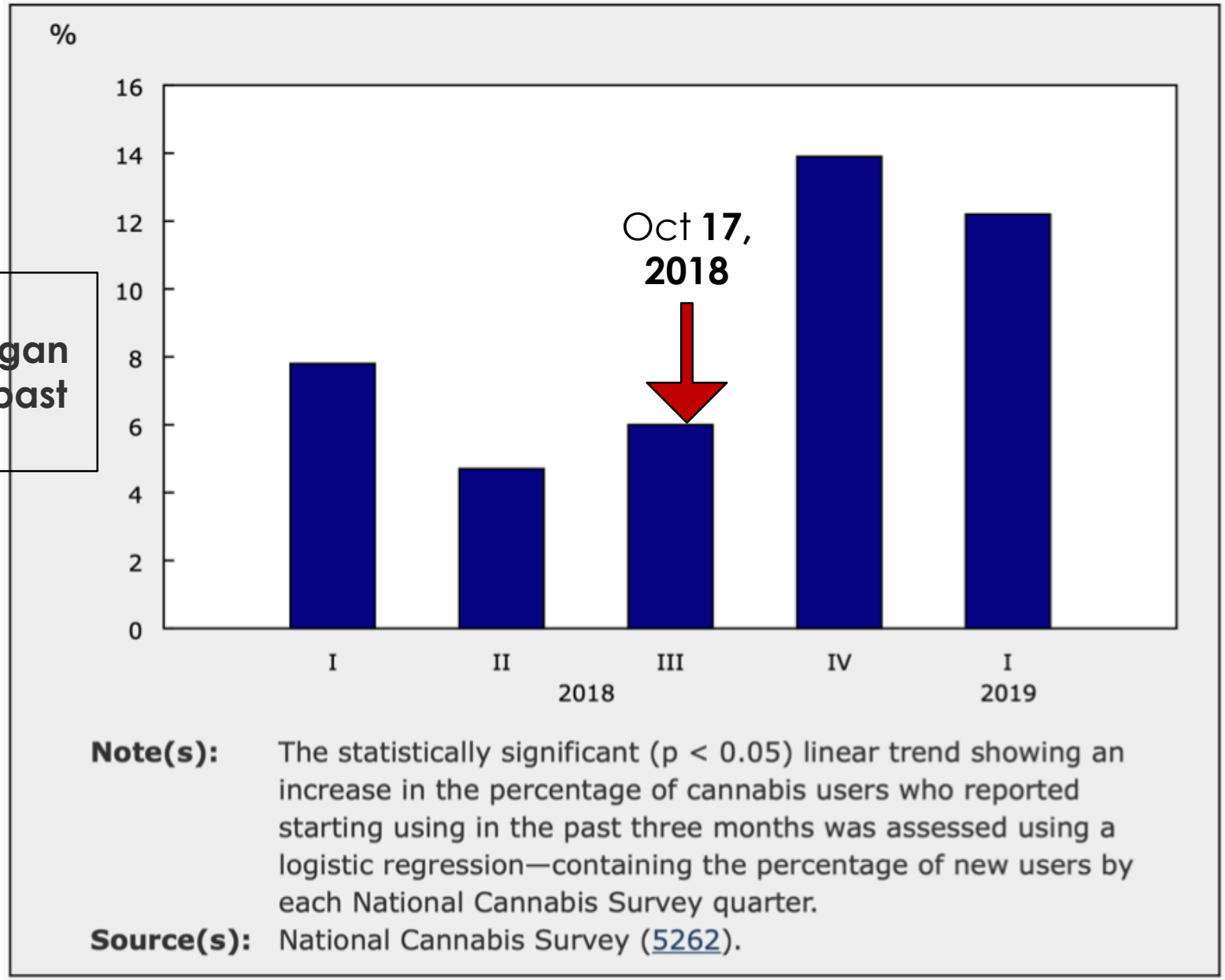
University of Manitoba

Cannabis use in the past 3 months



https://www150.statcan.gc.ca

% of cannabis users reporting that they **began using cannabis in the past 3 months** by quarter



"…there is a compelling reason to screen for cannabis use as a matter of routine in primary care and other health-care settings"

- Public Policy & Aging Report 2019

https://www150.statcan.gc.ca

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

BEST AVAILABLE **EVIDENCE**

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

Can Fam Physician 2018;64:111-20

WHERE DOESTHE EVIDENCE LIE?

Original Investigation

Cannabinoids for Medical Use

A Systematic Review and Meta-analysis

JAMA 2015;313(24):2456-2473

79 RCTs were included (No. or reports [No. of patients])[b]

- **28** Nausea and vomiting due to chemotherapy (37 [1772])
- **28** Chronic pain (63 [2454])
- **14** Spasticity due to multiple sclerosis or paraplegia (33 [2280])
- **4** HIV/AIDS (4 [255])
- **2** Sleep disorder (5 [54])
- **2** Psychosis (9 [71])
- **2** Tourette syndrome (7 [36])
- **1** Anxiety disorder (1 [24])
- **1** Glaucoma (1 [6])
- **0** Depression

n=6506

n=446

HOUSTON, WE HAVE A FEW PROBLEMS

79 trials: → 5% low risk of bias
→ **70% high risk of bias**
→ 25% unclear risk of bias

- Many studies enrolled patients with **history of cannabinoid use**
  → may exaggerate benefit & minimize adverse events
- **Unblinding** was very common (~90%) for patients and caregivers, regardless of cannabinoid type and dose

VIEWPOINT

The Achilles Heel of Medical Cannabis Research—Inadequate Blinding of Placebo-Controlled Trials

JAMA Intern Med. 2018;178(1):9-10

JAMA 2015;313(24):2456-2473

Can Fam Physician 2018;64:111-20

HOUSTON, WE HAVE A FEW PROBLEMS

- RCTs with **small sample sizes** & **short durations** were common
  - sensitivity analysis of chronic pain RCTs:
    - → **smaller & shorter**-duration RCTs were **positive**
    - → **larger & longer** RCTs found **no effect** (wear-off over time?)

This isn't new in the world of chronic pain…

Topical NSAIDS ***vs.* placebo** for OA (*CDSR* **2017** Issue 5. Art.No.: CD008609):

- ≥ 50% pain⬇ @ **< 6** weeks → NNT = **5**

6-12 weeks → NNT = **7-10**

BUT…

NNH (stopping drug due to AE) = **50**

JAMA 2015;313(24):2456-2473

Can Fam Physician 2018;64:111-20

Table 1. Medical cannabinoids' estimated benefit when treating chronic pain, chemotherapy-induced nausea and vomiting, or spasticity with GRADE rating of evidence

INDICATION	ESTIMATED BENEFIT: CANNABINOIDS	ESTIMATED BENEFIT: CONTROL (PLACEBO UNLESS INDICATED)	NNT	GRADE QUALITY OF EVIDENCE
Chronic pain (median follow-up 4 wk)				
• ≥ 30% reduction in chronic (neuropathic plus cancer) pain*	39%	30%	11	Very low
• ≥ 30% reduction in neuropathic pain	38%	30%	14	Very low
• ≥ 30% reduction in palliative pain	30%	23%	NS (approximately 15)†	Very low
• Change in chronic pain scales (possible score 0-10)‡	Baseline: approximately 6 Decrease: 1.2-1.6	Baseline: approximately 6 Decrease: 0.8	NA →Δ 0.4-0.8/10	Very low
Chemotherapy-induced nausea and vomiting (median follow-up 1 d)				
• Control of nausea and vomiting (cannabinoids vs placebo)	47%	13%	3	Moderate
• Control of nausea and vomiting (cannabinoids vs neuroleptics)	31%	16% (vs neuroleptics)	7	Low
Spasticity (median follow-up 6 wk)				
• Global impression of change	50%	35%	7	Low
• ≥ 30% improvement in spasticity	35%	25%	10	Low
• Change in spasticity (possible score 0-10)‡	Baseline: 6.2 Decrease: 1.3-1.7	Baseline: 6.2 Decrease: 1.0	NA →Δ 0.3-0.7/10	Very low

EFFICACY

Can Fam Physician 2018;64:111-20

WHAT ABOUT **FUNCTION**?

i.e. can cannabinoids help your patient get physical?

- *PAIN* 2018;159:1932–54
  - No impact on physical or emotional functioning (47 RCTs)

ALSO…

- *JAMA* 2015;313:2456-73
  - No difference in QoL (3 RCTs)

SAFETY

Table 2. Adverse events and estimated event rates for medical cannabinoids, with GRADE of evidence rated high

TYPE OF ADVERSE EVENT	CANNABINOID EVENT RATE, %	PLACEBO EVENT RATE, %	NNH
Overall	81	62	6
Withdrawal due to adverse events	11	Approximately 3%	14
Serious adverse events	NS	NS	NS
Central nervous system effects	60	27	4
"Feeling high"	35	3	4
Sedation	50	30	5
Speech disorders	32	7	5
Dizziness	32	11	5
Ataxia or muscle twitching	30	11	6
Numbness	21	4	6
Disturbance in attention or disconnected thoughts	17	2	7
Hypotension	25	11	8
Dysphoria	13	0.3	8
Psychiatric	17	5	9
Euphoria	15	2	9
Impaired memory	11	2	12*
Disorientation or confusion	9	2	15
Blurred vision or visual hallucination	6	0	17
Dissociation or acute psychosis	5	0	20

recall the NNT?

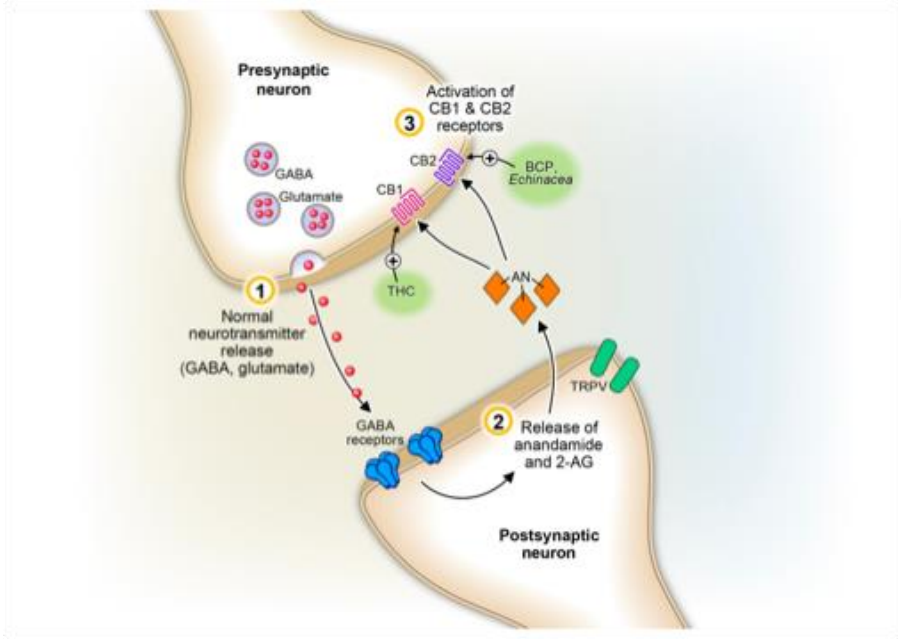
JAMA 2015;313(24):2456-2473

	No. of Studies (No. of Patients)	Summary OR (95% CI)	I^2, %
Psychiatric disorders	8 (1672)	3.10 (1.81-5.29)	55
Nervous system disorders	10 (1521)	3.17 (2.20-4.58)	46

Can Fam Physician 2018;64:111-20

PSYCHIATRIC EFFECTS

- Do cannabinoids have a role in treating mental illness: **NO**
  (*Lancet Psych* 2019;6: 995–1010)
  - Might they in the future



The Current

People skipping doctors and using CBD oil for bipolar disorder 'not treated at all,' warns expert

More clinical trials needed into cannabidiol's alleged health benefits: researcher

CBC Radio · Posted: Aug 23, 2019 12:11 PM ET | Last Updated: August 23

CBD oil is a cannabis extract that is non-psychoactive and does not produce a high. (Mike Segar/Reuters)

Mayo Clin Proc 2019;94(9):1840-1851

PSYCHIATRIC EFFECTS

- Are they associated with adverse psychiatric effects: **YES**
  - Broadly speaking → **NNH = 9** (*Can Fam Physician* 2018;64:111-20)
  - Acute psychiatric symptoms
    - Colorado ED visit study (Monte, *Ann Intern Med* 2019)(n=2567)

Table 2. Most Common Clinical Conditions Associated With Cannabis-Attributable Visits, by Route of Exposure

Condition	Edible Exposure (n = 238), n (%)	Inhalable Exposure (n = 2329), n (%)	Absolute Difference (Edible − Inhalable) (95% CI), *percentage points*	Total Visits, n (%)
Gastrointestinal symptoms	36 (15.1)	752 (32.3)	−17.2 (−12.2 to −22.1)	788 (30.7)
Cannabinoid hyperemesis syndrome	20 (8.4)	420 (18.0)	−9.6 (−5.7 to −13.5)	440 (17.1)
Intoxication	115 (48.3)	647 (27.8)	20.5 (13.9 to 27.1)	762 (29.7)
Psychiatric symptoms	62 (26.1)	571 (24.5)	1.6 (−4.2 to 7.4)	633 (24.7)
Acute psychiatric symptoms	43 (18.0)	254 (10.9)	7.1 (2.1 to 12.1)	297 (46.9)
Acute exacerbation of underlying chronic disease	1 (0.4)	93 (4.0)	−3.6 (−2.5 to −4.7)	94 (14.1)
Chronic psychiatric condition	1 (0.4)	99 (4.3)	−3.9 (−2.8 to −5.0)	100 (15.8)
Cardiovascular symptoms	19 (8.0)	73 (3.1)	4.9 (1.4 to 8.4)	92 (3.6)

Including acute anxiety & psychosis

2014-2016: **Edible products = 10.7%** of cannabis-attributable visits, but represented only **0.32%** of total cannabis sales in Colorado

The New York Times

Jan 17, 2019

Does Marijuana Use Cause Schizophrenia?

Schizophr Bull 2016 MA (10 studies (n=66 816)) + *Lancet Psych* 2019 (n=901 cases):

- **Risk of SCHIZOPHRENIA/OTHER PSYCHOSIS outcomes *vs.* nonusers**

Odds Ratios:

→ any cannabis use = **~2-3**

→ "most severe cannabis users" = **~4**

→ ≥ daily use of high-potency THC = **~5**

Population lifetime risk of schizophrenia = ~0.7%

✚ cannabis may exacerbate symptoms of those with schizophrenia

Association is not the same as causation

All observational studies → **so** many potential confounders

But, fairly consistent findings … *there may be something going on here*

Lancet Psych 2019;6: 427–36
Schizophr Bull vol. 42 no. 5 pp. 1262–1269, 2016
Addiction 2017; 112, 1653–1657

JAMA Psychiatry 2016;73:731-740

Key Points

Question Is persistent cannabis use for up to 20 years associated with physical health problems (periodontal health, lung function, systemic inflammation, and metabolic health) in early midlife?

Findings In this prospective, longitudinal study of a representative birth cohort of 1037 individuals, persistent cannabis use from ages 18 to 38 years was not associated with physical health problems at age 38 years with one exception: persistent cannabis use was statistically significantly associated with poor periodontal health.

Meaning Persistent cannabis use for up to 20 years is, for the most part, not associated with physical health problems in early midlife.

J Periodontol 2017;88:273-280
Brit Dent J 2016;220:597-601
JAMA 2008;299(5):525-531…

- Less brushing & flossing
- Less dental visits

] vs. non-users

- Dry mouth in up to 70% → **why?**

Consistent findings of:

↑ probing depth
↑ attachment loss

→ **1.5-2X risk** of severe periodontitis, especially in frequent users

↑ tooth decay

BROADER IMPLICATIONS

THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS

COMMITTEE'S CONCLUSIONS January 2017

CONCLUSIONS FOR: INJURY AND DEATH

There is substantial evidence of a statistical association between cannabis use and:

- Increased risk of motor vehicle crashes (9-3)

Risk of MVA ↑ ~2.5-3X

Risk of fatal MVA ↑ ~2X

18% of daily users believe it's safe to do so within **3h** → 15% of users report driving within **2h** of consuming

Nearly 20% reporting driving after consuming **cannabis** indicated they had also consumed **alcohol**

Canadian Guidelines on Cannabis Use Disorder Among **Older Adults** (2019) →

RECOMMENDATION #10:

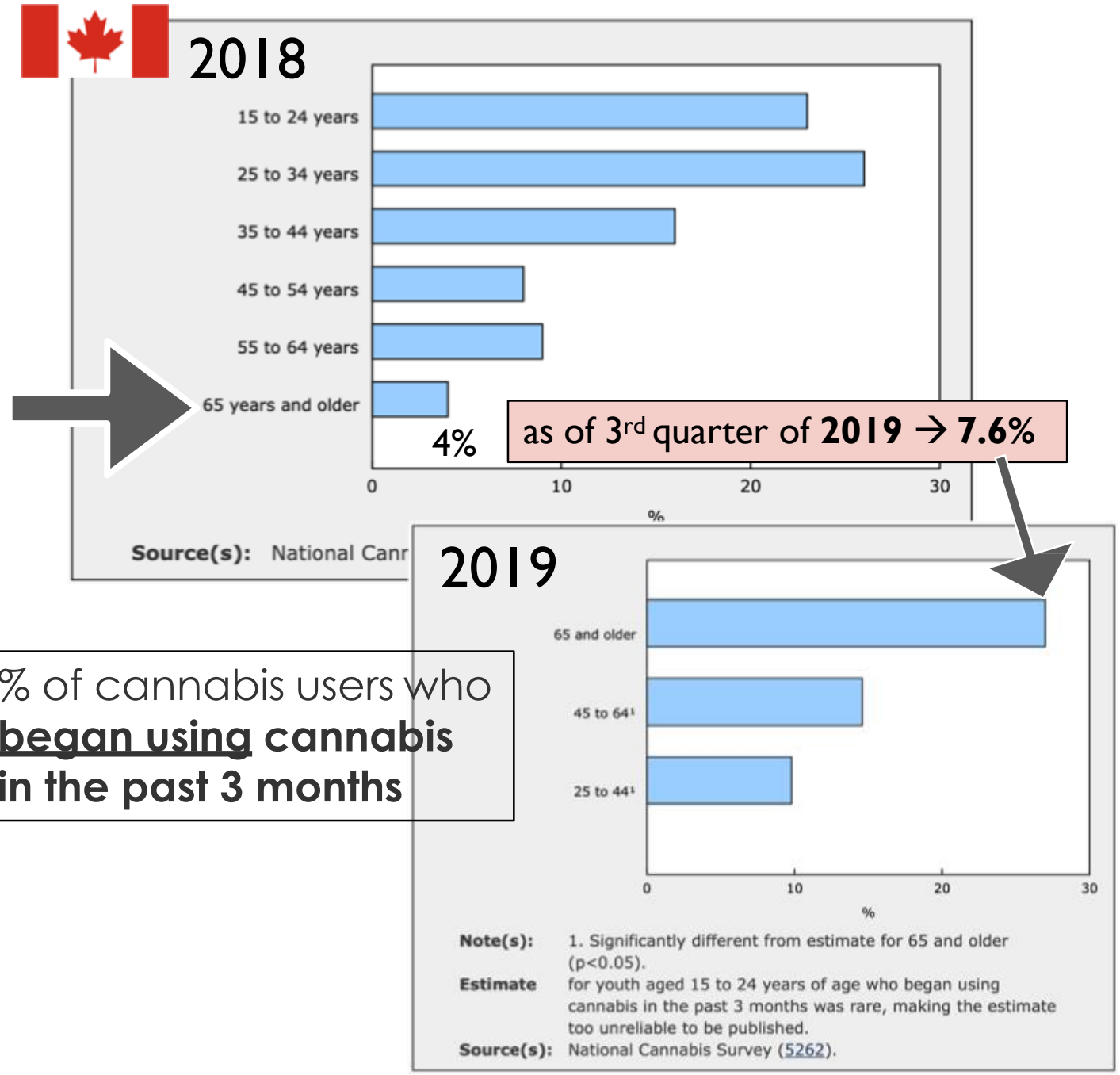
Clinicians should advise patients, caregivers, and families that:

a) Cannabis may impair the ability to safely drive a motor vehicle for up to 24 hours. [GRADE: Evidence: High; Strength: Strong]

https://www150.statcan.gc.ca

CANNABIS…
TIMES HAVE
CHANGED

Cannabis use in the past 3 months



% of cannabis users who **began using cannabis in the past 3 months**

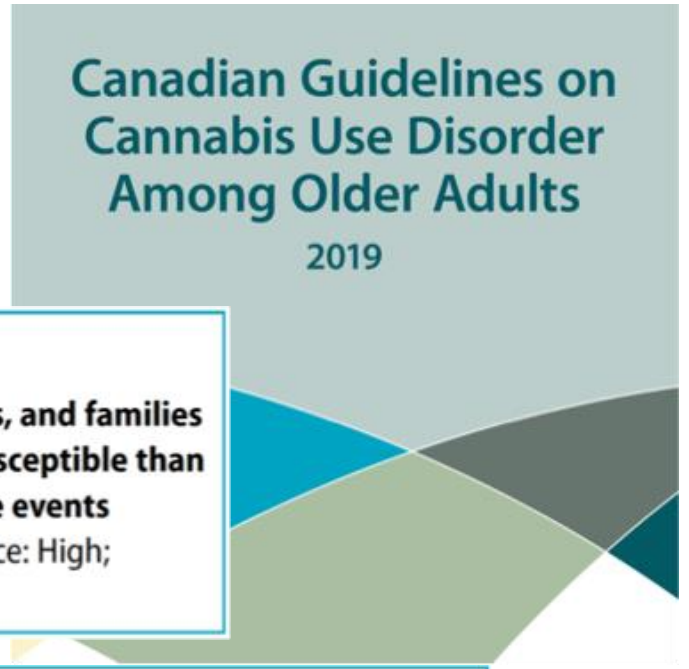
OLDER ADULTS

Is this concerning?

- Changes in metabolism & fat %
- High rates of medication use → higher risk for drug interactions
- More vulnerable physiology → increased sensitivity to psychoactive or CV effects

  e.g. dizziness, cognition, depth perception, falls, etc.

*ASK about cannabinoid use



RECOMMENDATION #4:

Clinicians should counsel patients, caregivers, and families to be aware that older adults can be more susceptible than younger adults to some dose-related adverse events associated with cannabis use. [GRADE: Evidence: High; Strength: Strong]

RECOMMENDATION #8:

Clinicians should educate patients on the risk of cannabis-induced impairment especially if the patient is cannabis-naive or titrating to a new dose. It is recommended that the starting dose should be as low as possible and gradually increased over time if needed. [GRADE: Evidence: High; Strength: Strong]

RECOMMENDATION #13:

All patients regardless of age should be screened for:

a) The use of non-medical and medically authorized cannabis and cannabinoids, and illicit synthetic cannabinoids as well as tobacco, alcohol, and other drugs. [GRADE: Evidence: Low; Strength: Strong]

PERSPECTIVE

medscape.com Oct/Nov, 2019

Dr. MICHAEL ATKINS 2 days ago

If we are to change practice simply because of patient anecdotes, then you will definitely want to prescribe more cigarettes. Oh, and more alcohol, particularly the inexpensive kind, the Boone's farm, Mad Dog 20/20, Ripple, etc.

And definitely prescribe more opioids. Be sure to prescribe more Oxys, patients will tell you, emphatically, they can't live without these substances.

The single common denominator of all substance that are abused is the patient's firmly held belief that life is much better for them with, than without the substance, and there is no way on earth to cope without it.

rxfiles.ca

A final thought: *If a patient told you they were getting benefit from ibuprofen over-the-counter, you might recommend they continue taking it. You might even prescribe it. But would you feel the same way if the patient was using 6 grams of ibuprofen per day? Or if the patient insisted that the ibuprofen was improving their blood sugar control? Or if the patient had a history of GI bleeds?*

PUBLIC ASSUMPTIONS & SIGNIFICANT UNCERTAINTIES

does nabilone/nabiximols = medical cannabis

does CBD = better

does CBD = safer

CBD…

- Although important preclinical and pilot human studies have suggested a potential role for CBD in numerous clinical situations, thorough clinical studies have only been performed on intractable epilepsy syndromes for which Epidiolex, a CBD drug, was approved by the US Food and Drug Administration for use.

- Controlled studies for Lennox-Gastaut & Dravet syndromes:
  - **ALT elevations** >3X ULN → **13%** in EPIDIOLEX group *vs.* **1%** on placebo
- Epilepsy trials:
  - **somnolence, decreased appetite, pyrexia, diarrhea** in up to **36%**
- Underappreciated **psychotropic effects**?
  - *vs.* placebo (mostly pediatric epilepsy trials → CBD ~**10-20mg/kg/day**): aggression/anger **3-5% *vs.* <1%**; irritability/agitation **5-9% *vs.* 2%**; somnolence **25% *vs.* 8%**

Consider:
Sativex **max** daily dose = CBD **30mg**

rxfiles.ca
Br J Clin Pharmacol 2019;85:1888–1900
Mayo Clin Proc 2019;94:1840-1851

DRUG **INTERACTIONS**

Rxfiles.ca

DI: **A note on drug interactions**: Interactions are not fully understood; many are theoretical. Cannabis has many compounds besides THC & CBD; these may have unknown drug interactions. Watch closely for **pharmacodynamic** (additive) interactions.

All cannabinoids: additive CNS effects (e.g. sedation, confusion, impairment) with alcohol, anticholinergics, anti-epileptics, benzos, opioids, etc. [?disulfiram-rx if alcohol in product]

THC-containing products 2C9 & 3A4 substrate: ↓ levels by CBZ, SJW, phenytoin, etc.
↑ levels by clarithromycin , fluoxetine, fluvoxamine, gemfibrozil, etc.

CBD-containing products 2C19 & 3A4 substrate: ↓ levels by CBZ, SJW, phenytoin, etc.
↑ levels by clarithromycin, fluconazole, fluvoxamine, gemfibrozil, etc.
2C19 inhibitor: ↑ levels of citalopram, **clobazam**; ↓ levels of clopidogrel
?additive hepatotoxicity risk with valproic acid or clobazam[19,20]

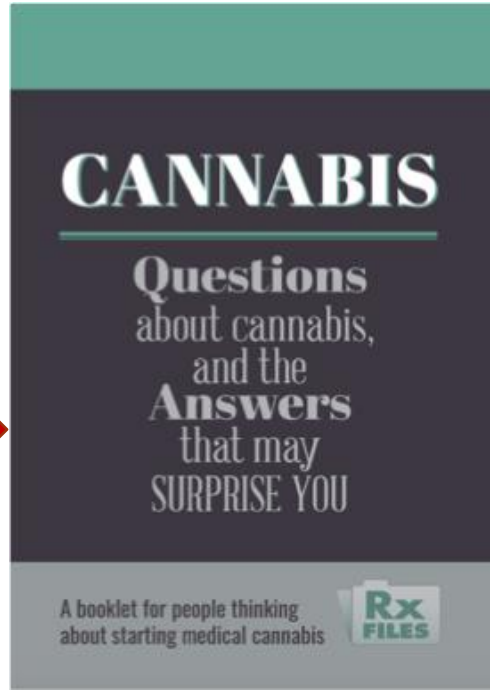
Smoked cannabis: smoking may result in 1A2 induction;
e.g. ↓ levels of antipsychotics, caffeine, TCAs, theophylline, warfarin

Nabilone: while a THC-mimic, does not have THC drug interactions.

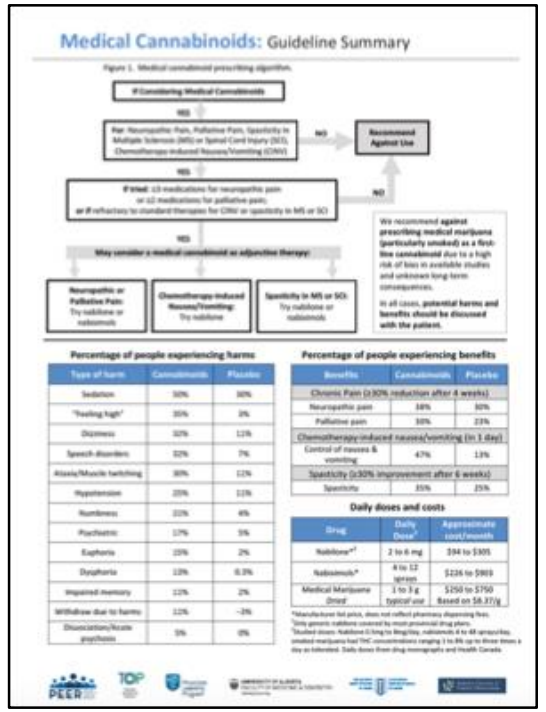
* ASK about cannabinoid use

RESOURCES

* Rxfiles Q&A (for patients) and charts (for you)



* CFP primary care guideline & 1-pager



- The National Academies of Sciences, Engineering, and Medicine: The Health Effects of Cannabis and Cannabinoids (2017)
- Canadian Guidelines on Cannabis Use Disorder Among Older Adults (ccsmh.ca) (2019)
- StatsCan ongoing tracking and infographics

  https://www150.statcan.gc.ca/n1/pub/13-610-x/cannabis-eng.htm

QUESTIONS

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THE SOLUTION TO THE OPIOID CRISIS?

Bradford (2018)

JAMA Internal Medicine | Original Investigation | HEALTH CARE POLICY AND LAW

Association Between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population

- 23M daily opioid doses/state/year
  - → If MCL, dropped by **~2M daily doses/year**

McMichael (2019)

March 27, 2019 | Number 156 https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3320778

The Impact of Cannabis Access Laws on Opioid Prescribing

→ MME decreased by **6.1 – 6.9%**