Cannabis

Dalhousie Spring Refresher
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Speaker Disclosure

No conflict of interest
Objectives

• Describe the benefits of cannabis
• Describe the risks of cannabis
• Conduct a medicinal cannabis trial
Agenda

- Pharmacology
- Evidence for benefit
- Evidence for harm
- Medicinal cannabis trial
Agenda

- Pharmacology
- Evidence for benefit
- Evidence for harm
- Medicinal cannabis trial
Cannabis sativa

- >100 phytocannabinoids
- >460 chemical compounds
- $\Delta^9$-Tetrahydrocannabinol (THC)
  - Partial agonist at CB receptor
  - Modulated by other cannabinoids
- Cannabidiol (CBD)
  - Inverse agonist (decreases THC activity)
  - Modulates some undesirable effects of THC
  - Not intoxicating
  - Not sedating

Robson, 2014, Drug Test Anal
Borgelt et al, 2013, Pharmacotherapy
## Cannabis Potency

<table>
<thead>
<tr>
<th>Form</th>
<th>Source</th>
<th>THC content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>Dried leaves/flowers/seeds</td>
<td>1-3% (10 mg/joint)</td>
</tr>
<tr>
<td></td>
<td>60’s and 70’s</td>
<td>6-20% (60-150 mg/joint)</td>
</tr>
<tr>
<td></td>
<td>80’s and 90’s</td>
<td>22-27%</td>
</tr>
<tr>
<td></td>
<td>2017</td>
<td></td>
</tr>
<tr>
<td>Hashish</td>
<td>Resin secreted by plant</td>
<td>10-20%</td>
</tr>
<tr>
<td>Hashish oil</td>
<td>Extracted by solvents</td>
<td>15-30% (up to 65%)</td>
</tr>
<tr>
<td>“shatter”</td>
<td>Extraction by butane</td>
<td>80-90%</td>
</tr>
</tbody>
</table>

CBD levels declining

Ashton, 1999, Br J Anaesth
Cannabis Potency

- USA 1995 to 2014
  - Illicit cannabis seized, n=38,681

<table>
<thead>
<tr>
<th>Year</th>
<th>% THC</th>
<th>% CBD</th>
<th>THC/CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>3.96 (±1.82)</td>
<td>0.28 (±0.48)</td>
<td>14.1</td>
</tr>
<tr>
<td>2014</td>
<td>11.84 (±6.60)</td>
<td>0.15 (±0.40)</td>
<td>76.5</td>
</tr>
</tbody>
</table>

**Change**
- % THC: ↑ 300%
- % CBD: ↓ 50%
- THC/CBD: ↑ 543%

Endocannabinoid System

- 600 million year old signaling system
  - Predates the cannabis plant
- Negative feedback system
- Regulates neuronal excitability and inflammation
- Integral part of central homeostasis and neuroprotection
- Fine control of wide range of physiologic functions

Aggarwal, 2013, Clin J Pain
Cannabis Pharmacokinetics

- Plasma half life: 56 hours occasional user
  28 hours regular user
- Tissue half life: 7 days
  - due to accumulation in fat
- Complete elimination of single dose up to 30 days
  - repeated doses results in drug accumulation

Ashton, 1999, Br J Anaesth
Cannabis Pharmacokinetics

• Metabolized in liver
  – 80 metabolites, some psychoactive
  – many with plasma half lives of 50 hours

• Active and inactive metabolites excreted in intestine and bile
  – 15% reabsorbed, further prolonging cannabis action

Ashton, 1999, Br J Anaesth
Agenda

• Pharmacology
• Evidence for benefit
• Evidence for harm
• Medicinal cannabis trial
Patient Reported Benefits of Medicinal Cannabis

- California, n=1,746
- Consecutive admissions to 9 assessment clinics
- To relieve:  
  - Pain: 82.6%
  - Muscle Spasms: 41.1%
  - Headaches: 40.7%
  - Anxiety: 37.8%
  - Nausea/Vomiting: 27.7%
  - Depression: 26.1%
  - Cramps: 19.0%
  - Panic Attacks: 16.9%

Reinarman et al, 2011, J Psychoactive Drugs
Patient Reported Benefits of Medicinal Cannabis

<table>
<thead>
<tr>
<th>To improve:</th>
<th>Sleep</th>
<th>70.7%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relaxation</td>
<td>55.1</td>
</tr>
<tr>
<td></td>
<td>Appetite</td>
<td>37.7</td>
</tr>
<tr>
<td></td>
<td>Concentration/Focus</td>
<td>22.9</td>
</tr>
<tr>
<td></td>
<td>Energy</td>
<td>15.9</td>
</tr>
</tbody>
</table>

| To prevent:            | Medication Side Effects | 22.5 |
|                        | Anger            | 22.4  |

| To substitute for:     | Prescription Medications | 50.9 |
|                        | Alcohol           | 13.0  |

Reinarman et al, 2011, J Psychoactive Drugs
Medicinal Cannabis Trials

• Properly designed trials very difficult to achieve
  – Illicit substance
  – Adequate placebo almost impossible to find
  – Large inter-individual variability in absorption, both inhaled and oral

Killestein et al, 2004, Drugs
Cannabinoid Trials

- Nabiximols: 6000 patient years
- Cannabis: 3 patient years
Cannabis for CNCP – Systematic Review

6 RCT’s

• 5 cross-over designs
  – High quality

• 1 pain secondary outcome in MS spasticity study

• Time 6 hours to 5 days, total n=226

• THC content 0% to 9.4%

• Meta-analysis not possible

Deshpande et al, 2015, Can Fam Phys
Cannabis for CNCP – Systematic Review

• Clinically meaningful outcome met in 3 of 6 studies
  – Decrease of 2 points on 0 to 10 scale or 30% improvement in pain intensity
• No functional assessment in any trial
• All compared to placebo, none compared to other standard treatments
• No serious adverse events
  – Cannabis greater number of adverse events than placebo in all studies

Deshpande et al, 2015, Can Fam Phys
Cannabis for CNCP – Systematic Review

• Conclusions
  – Low dose smoked cannabis associated with improvement in refractory neuropathic pain of moderate severity in patients using concurrent analgesics
  – Neurocognitive side effects common
  – Long term consequences unknown

Deshpande et al, 2015, Can Fam Phys
## Cannabis for Neuropathic Pain

- Randomized, double-blind, placebo-controlled study
- Inhaled cannabis (2.9%, 6.7%), 2 to 4 puffs
- Spinal cord neuropathic pain, n=42, t=8 hours

<table>
<thead>
<tr>
<th>VAS</th>
<th>≥30%</th>
<th>95%CI</th>
<th>p</th>
<th>nnt</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>placebo</td>
<td>45%</td>
<td>31-60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.9%</td>
<td>70%</td>
<td>54-83</td>
<td>.02</td>
<td>4</td>
<td>2.1-25.3</td>
</tr>
<tr>
<td>6.7%</td>
<td>88%</td>
<td>74-95</td>
<td>&lt;.001</td>
<td>3</td>
<td>1.6-4.2</td>
</tr>
</tbody>
</table>

- Dose-dependent increase in psychoactive side effects
- No difference in cognitive function

Plant-Based Cannabis for Chronic Pain

• Systematic review
  – 13 systematic reviews
  – 62 primary studies
• May alleviate neuropathic pain in some patients (low evidence – 13 trials)
• Insufficient evidence for other pain

Cannabis for Neuropathic Pain

• Cochrane review
  – randomized, double-blind controlled trials
• Very low quality studies
• Uncertain pain reduction
• Harms may outweigh benefits

Mucke et al. Cochrane Database Syst Rev. 2018;3:CD012182
Cannabis for MS Spasticity

- Randomized, double-blind, placebo-controlled crossover trial
- \( n = 30 \), 3 days
- Once daily inhaled cannabis vs placebo

<table>
<thead>
<tr>
<th>Mean difference</th>
<th>cannabis</th>
<th>placebo</th>
<th>effect</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasticity</td>
<td>2.95</td>
<td>0.21</td>
<td>2.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>↓ cognition</td>
<td>8.32</td>
<td>-0.35</td>
<td>8.67</td>
<td>=0.003</td>
</tr>
<tr>
<td>“high”</td>
<td>6.43</td>
<td>1.39</td>
<td>5.04</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Corey-Bloom et al, 2012, CMAJ
Cannabis for Anxiety and Mood Disorders

- Literature review
- No RCT’s
- Adverse effects
  - Anxiety
  - Psychosis
  - Neurocognitive impairment
  - Addiction

Turna et al. Depress Anxiety. 2017;34:1006-1017
Cannabis for PTSD

• Systematic review
  – 2 systematic reviews: insufficient evidence
  – 3 observational studies: no benefit

• No RCT’s
  – 2 RCT’s and 6 other studies ongoing

• Insufficient evidence to draw conclusions about the benefits and harms

Cannabis for Chemotherapy-Induced Nausea/Vomiting

- Literature review
  - 3 systematic reviews
- No clinical trials
- Not recommended

Cannabis for Headaches

• Literature review
• Insufficient evidence for the use of cannabis for headaches

Medicinal Cannabis and Opioid Overdose

- Age-adjusted opioid analgesic overdose death rate per 100,000 population in each state with medical Cannabis program – 1999 to 2010
- 13 states
- 24.8% lower mean annual opioid overdose mortality rate (95% CI −37.5% to −9.5%) p=.003

Bachhuber et al. JAMA Int Med. 2014;174:1668
Cannabis and Opioid Sparing

• Systematic review
  – 9 clinical studies
  – Meta-analysis not possible

• No RCT’s that provide evidence of an opioid-sparing effect of cannabis

Cannabis in CNCP Patients Prescribed Opioids

• Prospective, observational cohort study
  – $N=1514$, $t=4$ years
• 24% used cannabis for pain
• No reduction in oral morphine equivalent
• No increased opioid discontinuation

CBD for Seizures

Severe treatment-resistant pediatric seizures

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>time</th>
<th>20mg/kg</th>
<th>placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lennox-Gastaut</td>
<td>171</td>
<td>14 wk</td>
<td>43.9%</td>
<td>21.8%</td>
<td>=.0135</td>
</tr>
<tr>
<td>Lennox-Gastaut</td>
<td>225</td>
<td>14 wk</td>
<td>41.9%</td>
<td>17.2%</td>
<td>=.005</td>
</tr>
<tr>
<td>Dravet</td>
<td>120</td>
<td>14 wk</td>
<td>38.9%</td>
<td>13.3%</td>
<td>=.01</td>
</tr>
</tbody>
</table>

Evidence for Benefits

• Neuropathic pain
  – HIV neuropathy, MS pain, CRPS, spinal cord injury, diabetic neuropathy, traumatic or surgical peripheral nerve injury

• Severe treatment-resistant pediatric seizures (CBD)
Agenda

• Pharmacology
• Evidence for benefit
• Evidence for harm
• Medicinal cannabis trial
Cannabis Acute Effects

- Euphoria
- Laughter
- Talkativeness
- Sedation
- Distortion of time perception
- Increased perception external stimuli
- Increased appetite
- Dry mouth
- Tachycardia
- Increased blood pressure
- Bronchodilation
- Impaired motor co-ordination
- Impaired reaction time

- Dysphoria
- Anxiety
- Panic attacks
- Paranoia
- Hallucinations
- Disorganized thoughts
- Impaired memory
- Impaired attention and judgment
- Depersonalization
- Disorinetation
- Delusions
- Emotional lability
- Psychosis

Panlilio et al, 2015, Clin Pharmacol Ther
Cannabis Acute Effects

Euphoria
Laughter
Talkativeness
Sedation
**Distortion of time perception**
Increased perception external stimuli
Increased appetite
Dry mouth
Tachycardia
Increased blood pressure
Bronchodilation
**Impaired motor co-ordination**
**Impaired reaction time**

Dysphoria
Anxiety
Panic attacks
Paranoia
Hallucinations
Disorganized thoughts
Impaired memory
**Impaired attention and judgment**
Depersonalization
Disorinetation
Delusions
Emotional lability
Psychosis

Panlilio et al, 2015, Clin Pharmacol Ther
Cannabis and Driving

• Negatively affects
  – concentration and attentiveness
  – perception of time, speed and distance
  – ability to draw on information obtained from experiences
  – co-ordination on divided attention tasks

• Results in impaired motor performance in both driving simulator and on-the-road tests

Phillips et al. Workplace Health Safety. 2015:63;139-164
Cannabis and Driving

• Meta-analysis
  – 21 observational studies
  – N=239,739

• OR = 1.36 (95% CI 1.15–1.61)

Rogeberg et al. Addiction, 2016;111:1348
Cannabis and Driving

- Meta-analysis
  - 9 observational studies
  - experimental or simulator studies excluded

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.92</td>
<td>1.35-2.73</td>
<td>0.0003</td>
</tr>
<tr>
<td>Fatal</td>
<td>2.10</td>
<td>1.31-3.36</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Asbridge et al. BMJ. 2012 Feb 9;344:e536
Cannabis Use Disorder

• 9% all cannabis users
  – 30 to 40% daily cannabis users
• 38% medicinal cannabis users
  – 22% mild CUD (abuse)
  – 16% moderate to severe CUD (addiction)

Cannabis and Addiction

• Prospective longitudinal study
• Association of cannabis use and addiction
• n=34,653, t=3 years
• Cannabis use significantly associated with:
  – SUD  OR=6.2 (95%CI 4.1-9.4)
  – CUD  OR=9.5 (95%CI 6.4-14.1)

Blanco et al, 2016, JAMA Psychiatry
Cannabis Withdrawal: DSM-V

3 or more within one week of abrupt cessation of prolonged cannabis use

• Irritability, anger, or aggression
• Nervousness or anxiety
• Sleep difficulty (eg, insomnia or vivid dreaming)
• Decreased appetite or weight loss
• Restlessness
• Depressed mood
• Physical symptoms causing discomfort: at least one of
  – abdominal pain
  – shakiness/tremors
  – sweating
  – fever
  – chills
  – headache

Brezing et al. Neuropsychopharmacology. 2018;43:173-194
CUD Treatment

• Motivational interviewing
• CBT
• Contingency management
• No approved pharmacotherapy
  – Nabilone
  – Nabiximols
  – Gabapentin
  – N-Acetylcysteine

Cannabis and Anxiety

- Meta-analysis
- 31 studies

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Association</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any use</td>
<td>1.24</td>
<td>1.06-1.45</td>
<td>=.006</td>
<td></td>
</tr>
<tr>
<td>CUD</td>
<td>1.68</td>
<td>1.23-2.31</td>
<td>=.001</td>
<td></td>
</tr>
<tr>
<td>Anxiety and Depression</td>
<td>Any use</td>
<td>1.68</td>
<td>1.17-2.40</td>
<td>=.004</td>
</tr>
</tbody>
</table>

Keidzior et al. BMC Psychiatry. 2014;14:136
Cannabis and Depression

- Meta-analysis
- 14 studies
- cannabis users vs controls
  - OR=1.17 (95%CI: 1.05–1.30)
- heavy cannabis vs non-users or light users
  - OR=1.62 (95%CI: 1.21–2.16)

Cannabis and Suicidality

- Systematic review
  - 20 studies, n=141,107

<table>
<thead>
<tr>
<th></th>
<th>Use</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideation any</td>
<td>1.43</td>
<td>1.13-1.83</td>
<td></td>
</tr>
<tr>
<td>heavy</td>
<td>2.53</td>
<td>1.00-6.39</td>
<td></td>
</tr>
<tr>
<td>Attempt any</td>
<td>2.23</td>
<td>1.24-4.00</td>
<td></td>
</tr>
<tr>
<td>heavy</td>
<td>3.20</td>
<td>1.72-5.94</td>
<td></td>
</tr>
<tr>
<td>Death any</td>
<td>2.56</td>
<td>1.25-5.27</td>
<td></td>
</tr>
</tbody>
</table>

Cannabis and Psychosis

- Meta-analysis
  - 10 studies, n=66,816
- Any cannabis use
  - OR 1.97 (95%CI 1.68-2.31)
- Heavy cannabis use
  - OR 3.90 (95%CI 2.84-5.34)
- Dose-response relationship
- Causal relationship unclear

Cannabis and Bipolar Disorder

• Systematic review, meta-analysis
• 6 studies, variable quality
  – n=2391, t=3.9 years
• meta-analysis of two studies
  – cannabis use is associated with an a 3-fold increased risk for the new onset of manic symptoms
  – Odds Ratio: 2.97 (95%CI, 1.80–4.90)
• avoid cannabis use in youth and those with bipolar disorder

Gibbs et al, 2015, J Affect Disord
Cannabis and Psychosis

• Literature review and critical analysis
• Unequivocal association between cannabis use and psychosis
• Conclusion of review
  – Cannabis does not in itself cause psychosis
  – Early use and heavy use are more likely in individuals with a vulnerability to psychosis

Ksir et al, 2016, Curr Psychiatry Rep
Cannabis and Psychosis

• Meta-analysis
  – Effect of continued cannabis use after diagnosis
  – 24 studies, n=16,565

• Increased rates of relapse

<table>
<thead>
<tr>
<th>Compared to:</th>
<th>effect size</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-user</td>
<td>d = 0.36</td>
<td>0.22 to 0.50</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Discontinued user</td>
<td>d = 0.28</td>
<td>0.12 to 0.44</td>
<td>&lt;.0005</td>
</tr>
</tbody>
</table>

Cannabis, Cognition and Brain Function

• Systematic review
  – 56 studies

• Subtle cognitive deficits at 7 days
  – Executive functioning
  – Memory
  – Attention
  – Learning

• Persistent cognitive deficits – unclear

• Changes in hippocampus volume and grey matter density

Cannabis Hyperemesis Syndrome

• Essential for Diagnosis
  – Long-term cannabis use

• Major features
  – Severe cyclic nausea and vomiting
  – Abdominal pain: epigastric or periumbilical
  – Weekly use of marijuana
  – Resolution with cannabis cessation
  – Relief of symptoms with hot showers or baths

Cannabis Hyperemesis Syndrome

Treatment
• Standard antiemetics frequently ineffective
• Most effective treatment (based primarily on case series and reports):
  – Haloperidol
  – Benzodiazepines
  – Capsaicin cream

Cannabis and Cardiovascular Disease

• Cannabis use cause acute physiologic cardiovascular effects
  – hypertension
  – tachycardia
  – catecholamine release
  – vascular constriction

• Reports of young people suffering cardiovascular events shortly after smoking cannabis
Cannabis and Cardiovascular Disease

- Coronary Artery Risk Development in Young Adults study
- N=5113, t=27 years
  - 131,990 person-years
- 84% used cannabis
- No association with CVD, stroke or transient ischemic attacks, coronary heart disease, or CVD mortality

Cannabis and Cardiovascular Disease

• Systematic review - 115 studies
  – 81 case reports
  – 29 observational studies
  – 3 clinical trials
  – 2 experimental studies

• Limited data

• Association with CVD
  – strongest with ischemic stroke

Cannabis and Stroke

- Population survey
- N=7455

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any use</td>
<td>3.3</td>
<td>1.8-6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted</td>
<td>2.3</td>
<td>1.1-4.5</td>
<td>=0.02</td>
</tr>
<tr>
<td>≥Weekly</td>
<td>4.7</td>
<td>2.1-10.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cannabis and Respiratory Disease

- Smoke contains carbon monoxide, and the same tars, irritants and carcinogens as cigarettes
- Vaporization does not eliminate all potentially harmful polyaromatic hydrocarbons
- Depth of inhalation and length breath held greater than cigarettes
  - carbon monoxide blood levels x 5

Ashton, 1999, Br J Anaesth
Cannabis and Pulmonary Function

• Longitudinal study
  – n=5016, t=20 years
  – PFT=19,703
• No effect on pulmonary function with cannabis use of 7 joint years
  – 1 joint a day for 7 years
• Insufficient numbers for effect with high exposure

Pletcher et al. JAMA. 2012;307:173
Cannabis and Respiratory Disease

- Systematic review
  - 48 studies
- **Cancer** – 12 studies
  - 8 studies increased risk (2.1 to 4.1)
- Association with bullous emphysema, spontaneous pneumothorax, and COPD
- Reported symptoms: wheezing, SOB, cough, altered PFT’s, phlegm, bronchodilation

Martinasek. Respir Care. 2016;61:1543-1551
Cannabis and Lung Cancer

- n=49,321, t=40 years
- 10.5 % reported lifetime use of marijuana
- 1.7 % used more than 50 times (“heavy use”)
- Adjusted for tobacco use, alcohol use, respiratory conditions, and socioeconomic status
- **HR 2.12** (95%CI 1.08–4.14) of developing lung cancer over the 40-year follow-up period for heavy users

Callaghan et al, 2013, Cancer Causes Control
Cannabis and Lung Cancer

• n=5144 (2159 with lung cancer)
• adjusted for socio-demographic factors, tobacco smoking status and pack-years
• Little evidence for an increased risk of lung cancer among habitual or long-term cannabis smokers

Zhang et al, 2015, Int J Cancer
Cannabis and Testicular Cancer

- Meta-analysis
- 3 studies, n=719
- Cannabis use associated with an increase in non-seminoma testicular cancer
  OR=2.59 (95%CI 1.60-1.49)

Gurney et al, 2015, BMC Cancer
Cannabis and Pregnancy

• Cannabis highly lipid soluble
  – Crosses placenta and blood-brain barrier
  – Accumulates in fetal brain

• Endocannabinoid system
  – present in embryonic CNS development at 16 to 22 days gestation
  – involved in shaping neuronal circuitry and modulating development of neurotransmitter systems
Cannabis Use in Pregnancy

• USA 2014
• In-person interviews
  – N=15,318
  – Past-month cannabis use
• Pregnant 3.85% (95%CI 2.87-5.18)
• Pregnant 18-25 7.47% (95%CI 4.67-11.93)

Brown et al. JAMA. 2017;317:207-209
Cannabis and Pregnancy

- Prospective study
- $N=24,874$ over 7 year period

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low birth weight</td>
<td>1.7</td>
<td>1.3-2.2</td>
</tr>
<tr>
<td>Preterm labour</td>
<td>1.5</td>
<td>1.1-1.9</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>2.2</td>
<td>1.8-2.7</td>
</tr>
<tr>
<td>NICU admission</td>
<td>2.0</td>
<td>1.7-2.4</td>
</tr>
</tbody>
</table>

Cannabis and Stillbirths

- Observational study
  - 570 stillbirths, 1050 live births
- **OR 2.34** (95% CI 1.13–4.81)

Varner et al. Obstet Gynecol. 2014;123:113
Cannabis and Breastfeeding

• Cannabis may reduce maternal milk production through prolactin inhibition
• 0.8% maternal cannabis ingested by newborn through breast milk
• 12% oral bioavailability
• Recommendation
  – Support breastfeeding
  – Provide education about potential risks
  – Encourage lowest cannabis use

Maternal Cannabis and IQ

• Prospective study
  – 10 year follow up
  – N=606

• 5.3% heavy users (> 1 a day) in 2\textsuperscript{nd} trimester
  – 9.4 point reduction in reading comprehension
  – p=0.001

Goldschmidt et al. Neurotoxicol Teratol. 2004;26:521
Maternal Cannabis and Child Behaviour

• Prospective study
  – 10 year follow up
  – N=636

• First and third trimester users, significant association with:
  – Hyperactivity
  – Impulsivity
  – Inattention
  – Delinquency

Maternal Cannabis and Neuropsychological Outcomes

• Prospective study
  – 10 year follow up
  – N=593

• Prenatal use had significant association with:
  – Learning
  – Memory
  – Impulsivity

Richardson et al. Neurotoxicol Teratol. 2002;24:309
Prenatal Cannabis Use and Conduct Disorders

• Meta-analysis
  – 3 RCT’s, n=1263
• OR 1.29 (95%CI 0.93–1.81)
• Conclusion:
  No overall effect of cannabis use during pregnancy on offspring conduct problems

Ruisch et al. Neurosci Biobehav Rev. 2018;84:325-336
Pediatric Cannabis Poisoning

• Retrospective cohort study, children under 10
  – Cannabis poisoning after legalization
• Median age 2 to 2.4 years
• 52% edibles, 47% recreational product

<table>
<thead>
<tr>
<th></th>
<th>2 yrs before</th>
<th>2 yrs after</th>
<th>% change</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>rate 95%CI</td>
<td>rate 95%CI</td>
<td>% 95%CI</td>
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<tr>
<td>Hospital/100,000 pop</td>
<td>1.2 2.6-6.9</td>
<td>2.3 1.6-3.3</td>
<td>100 10-265</td>
</tr>
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<td>Poison Centre /1000 cases</td>
<td>0.9 0.7-1.2</td>
<td>2.3 1.9-2.8</td>
<td>156 75-277</td>
</tr>
<tr>
<td>/100,000 pop</td>
<td>2.7 1.9-3.7</td>
<td>6.3 5.1-7.8</td>
<td>136 60-246</td>
</tr>
</tbody>
</table>

Wang et al. JAMA Pediatr. 2016;170:e160971
Medicinal Cannabis and Public Health

• Systematic review
• 28 studies
• Conclusion: medical cannabis unrelated to subsequent changes in cannabis use in the general population

Under 25

Increased risk of:

• cannabis use disorder
• illicit drug use
• suicidal ideation
• persistent psychosis
• long-term cognitive impairment
Cannabis Use and Risks in Adolescents

• Literature review
• Strong association between:
  Early, frequent, heavy use
  and
  Cognitive dysfunction
  Poor psychiatric outcomes

Evidence for Harm

- Motor vehicle accidents
- Cannabis use disorder
- Anxiety and mood disorders
- Psychosis
- Cognitive dysfunction
- Hyperemesis syndrome
- Cardiovascular disease
- Respiratory disease
- Pregnancy
- Poisoning

Risks of harm greater with age <25
Agenda

• Pharmacology
• Evidence for benefit
• Evidence for harm
• Medicinal cannabis trial
Indications

• Neuropathic pain
  – HIV neuropathy, MS pain, CRPS, spinal cord injury, diabetic neuropathy, traumatic or surgical peripheral nerve injury
  – Failed standard treatment
    • Non-pharmacologic
    • Pharmacologic

• Severe treatment-resistant pediatric seizures (CBD)
No Indication

Either studies have not been done, or there is insufficient evidence for use in:

Fibromyalgia
Osteoarthritis
Low back pain
Anxiety
PTSD
Insomnia
Irritable bowel D
Inflammatory bowel D
Appetite stimulation

Nausea/vomiting
MS spasticity
Movement disorders
Alzheimer's
ALS
Cancer
Glaucoma
HIV
Contraindications

- History of cannabis use disorder
- Active substance use disorder
- Age under 25
- Personal or strong family history of psychosis
- Unstable cardiovascular disease (angina, peripheral vascular disease, cerebrovascular disease, arrhythmias)
- Severe respiratory disease
- Pregnant, or planning to become pregnant
Prescribe with Caution

- Smokes tobacco
- Cardiovascular disease
- Active mood or anxiety disorder
- Heavy use of alcohol
- High doses of opioids, benzodiazepines or other sedating medications
Alcohol and Sedating Drugs

- Worsens the cognitive impairment caused by opioids, benzodiazepines, other sedatives, and alcohol
- Use alcohol in moderation
- Taper patients on high doses of opioids or benzodiazepines
• The College considers the authorization of marijuana for medical purposes to be a clinical act and an insured service. Physicians must not bill patients directly for services related to the authorization of marijuana for medical purposes, which includes the completion of any required forms.

• Physicians must only authorize the use of marijuana for medical purposes in the context of a bona fide patient-doctor relationship. Physicians may only authorize the use of marijuana for medical purposes when in direct, in-person contact with their patients.
Physician Responsibility

- Primary care-giver for condition requiring cannabis
- Full pain and risk assessment
- Regular follow up
OR
- Referral to specialized pain clinic
- Regular communication with consultant
Disagreements with Patient

- Cannabis is not an approved medicine
- There is little evidence for its benefit
- There are harms associated with its use
- It is only indicated for neuropathic pain
- There are contraindications for its use
Before Starting Cannabis

1. Adequate trials of
   - Non-pharmacologic therapies
   - Standard pharmacologic therapies
   - Pharmaceutical cannabinoids

2. Risk assessment
Risk Assessment

• Cannabis use disorder
• Other substance use disorder
• Urine drug screen
Cannabis Use Disorder - Screening

- CUDIT-R
- 8 items
  - How often
  - How many hours a day stoned
  - Inability to stop
  - Failing to do activities
  - Spending most of time around use
  - Problem with memory or concentration
  - Using in hazardous situations (driving)
  - Thought about cutting down
- 91% sensitivity, 90% specificity
- ≥ 13: moderate to severe CUD
- ≥ 9: mild CUD

Safe Use

- Use lowest dose necessary
- Use oil or with a vaporizer
- Do not use with alcohol or sedating drugs
- If inhaled:
  - do not mix with tobacco
  - avoid use in house to limit second-hand smoke
- Do not sell or give to others
- Store in locked container
Prescribing

- Goal of functional improvement and pain relief without euphoria or cognitive impairment
- Initiate trial like any other medication
  - Prescribe (authorize) monthly during initial titration
  - Monitor effect and side effects
  - Adjust dose monthly
Writing the Authorization

• Indicate concentration of THC
  – Prescribe products with low THC, high CBD
    • 1:20 THC:CBD
    • THC ≤ 9%
  – One joint contains about 500 mg THC

• Authorization written in grams of dried leaf
  – Stipulate to dispense as oil on form
  – Authorize 1 gm/day, but advise patient on dose titration
Dosing

• Start low, go slow
• Initial dose
  – 1 puff once a day
  – 0.1 ml oil tid
• Increase dose gradually
Dosing

• Most patients should require no more than 1 gm a day
• Maximum recommended dose 3 gm a day
• Health Canada approves doses up to 5 gm a day
• Consider discussion with experienced colleague for doses above 3 gm a day
Cannabis and Driving

Advise no driving:

• Four hours after inhalation
• Six hours after oral ingestion
• Eight hours if the patient experiences euphoria
Monitoring

- Functional improvement, pain reduction
- Cognitive and mood-altering effects
- Compliance with the dosing
- Compliance with administration
- Cannabis use disorder
- Use of any other substances
- Complications
- Urine drug screens
Discontinue Cannabis

- Failed cannabis trial
- Uses more than prescribed
- Uses cannabis from other sources
- Uses alcohol, opioids, or other substances problematically
- Show signs of cannabis use disorder
- Complications
Summary: Cannabis

- Limited evidence of benefit
- Many harms
  - Addiction
  - Anxiety and depression
  - Psychosis
  - Cognitive dysfunction
  - Cardiovascular and respiratory
  - Pregnancy
  - Driving
- Risks greater with age < 25 years
Summary: Cannabis

Indications

• Neuropathic pain
  – 3rd or 4th line
  – After non-drug treatments and standard drug treatments

• Treatment resistant, severe pediatric seizures (CBD)
Summary: Cannabis

Cannabis trial

• Conduct trial like any medication
  – Start low, go slow
  – Low THC, high CBD
  – Oil preferable
  – Maximum recommended dose 3 gm/day

• Monitor
  – Functional improvement
  – Complications

• Discontinue if failed trial or complications
Resources

• CFPC Cannabis Guideline
  – https://www.cfpc.ca/uploadedFiles/Resources/_PDFs/Authorizing%20Dried%20Cannabis%20for%20Chronic%20Pain%20or%20Anxiety.pdf

• Lower-Risk Cannabis Guideline

• Simplified Cannabinoid Guideline
  – https://www.cfp.ca/content/cfp/64/2/111.full.pdf

• Health Canada Cannabis Authorization form

• Cannabis Use Disorder Screening Tool