Cannabinoids

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Speaker Disclosure

No conflict of interest
Objectives

• Identify patients appropriate for cannabinoid therapy
• List the contraindications and complications of cannabinoid therapy
• Conduct a cannabinoid trial
Agenda

• Endocannabinoid system
• Pharmaceutical cannabinoids
• Medicinal cannabis
Cannabinoids

- Endocannabinoids
- Phytocannabinoids
- Synthetic cannabinoids
  - Pharmaceutical
  - Illicit
Endocannabinoids

- Anandamide
- 2-AG
Phytocannabinoids

• >100 in cannabis
  – Δ⁹-tetrahydrocannabinol (THC)
    • Weak partial agonist
  – Cannabidiol (CBD)
    • Decreases THC activity

• Nabiximols: SL cannabis extract
  – THC:CBD 1:1

• Cannador: oral cannabis extract

• Epidiolex: liquid plant-derived CBD
Pharmaceutical Synthetic Cannabinoids

- Nabilone: THC analog
  - 10 x potency of THC
- Dronabinol: synthetic THC
Illicit Synthetic Cannabinoids

- Spice, K2
- Survey of 15,000 worldwide – 17% have used
- Do not test +ve on cannabis UDS
- Major adverse effects
  - Psychosis, agitation, anxiety, paranoia
  - Acute kidney injury
  - Tachycardia
  - Myocardial infarction
  - Seizures
  - Hyperemesis

Available in Canada

• Nabiximols (Sativex©)
  – MS spasticity and pain not responsive to other therapy
  – Cancer pain not responsive to opioid therapy
• Nabilone (Cesamet©)
  – Severe nausea and vomiting due to cancer chemotherapy
• Medicinal cannabis
Endocannabinoid System

• 600 million year old signaling system
  – Predates the cannabis plant
• Regulates neuronal excitability and inflammation
• Integral part of central homeostatic modulatory system (neuroprotection)

Aggarwal, 2013, Clin J Pain
CB1 Receptors

- Most abundant G-protein coupled receptor in brain
  - 10 times μ-opioid
- NOT found in medullary respiratory centres
  - No overdose risk

Robson, 2014, Drug Test Anal
## CB1 Receptors - CNS

<table>
<thead>
<tr>
<th>Structure</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>Memory</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Co-ordination of motor function</td>
</tr>
<tr>
<td>Basal ganglion</td>
<td>Motor control</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>Thermal regulation, appetite, pituitary-hypothalamus-adrenal axis</td>
</tr>
<tr>
<td>Cerebral cortex</td>
<td>Cognitive function, emesis</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Emotions</td>
</tr>
<tr>
<td>Limbic centre</td>
<td>Reinforcement</td>
</tr>
<tr>
<td>Periaqueductal gray</td>
<td>Pain</td>
</tr>
</tbody>
</table>

Croxford, 2003, CNS Drugs  
Borgelt et al, 2013, Pharmacotherapy
# CB1 Receptors – Periphery

<table>
<thead>
<tr>
<th>Structure</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune cells</td>
<td>Immunity</td>
</tr>
<tr>
<td>Lymphoid tissue</td>
<td>Cell-mediated immunity</td>
</tr>
<tr>
<td>Small bowel</td>
<td>Emesis, motility</td>
</tr>
<tr>
<td>Lung smooth muscle</td>
<td>Bronchodilation</td>
</tr>
<tr>
<td>Eye ciliary body</td>
<td>Intra-ocular pressure</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>Skeletal muscles</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
</tr>
<tr>
<td>Peripheral nerves</td>
<td>Nociception</td>
</tr>
</tbody>
</table>

Croxford, 2003, CNS Drugs
Goutopoulos et al, 2002, Pharmacol Ther
## CB2 Receptors

<table>
<thead>
<tr>
<th>Structure</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Spleen</td>
<td></td>
</tr>
<tr>
<td>Thymus</td>
<td></td>
</tr>
<tr>
<td>Tonsils</td>
<td></td>
</tr>
<tr>
<td>Myeloid cells</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Macrophages</td>
<td></td>
</tr>
<tr>
<td>CNS astrocytes</td>
<td>Pain modulation</td>
</tr>
</tbody>
</table>

Martin Fontelles et al, 2008, CNS Drugs
Goutopoulos et al, 2002, Pharmacol Ther
Endocannabinoid System

• Relax
• Eat
• Sleep
• Forget
• Protect
## Changes in Endocannabinoid System in Pathologic States

<table>
<thead>
<tr>
<th>Disease</th>
<th>Changes in Endocannabinoid System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s</td>
<td>↑AEA substantia nigra, ↑AEA, ↓2-AG globus pallidus, ↑AEA cerebrospinal fluid</td>
</tr>
<tr>
<td>Alzheimer’s</td>
<td>↑2-AG hippocampus</td>
</tr>
<tr>
<td>ALS</td>
<td>↑AEA, ↑2-AG spinal cord</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>↓AEA, ↓2-AG striatum and midbrain</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>↑AEA hippocampus</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>↑endocannabinoids periaqueductal grey, ventral medulla, spinal cord</td>
</tr>
</tbody>
</table>

Di Marzo et al, 2007, Curr Opin Lipidol
Changes in Endocannabinoid System in Pathologic States

<table>
<thead>
<tr>
<th>Condition</th>
<th>Endocannabinoid Changes</th>
</tr>
</thead>
</table>
| Obesity                       | ↑2-AG adipocytes
                               | ↑AEA, 2-AG pancreas
                               | ↑AEA liver               |
| Colon inflammation            | ↑AEA colon              |
| Diverticular disease          | ↑AEA colon              |
| Eating disorders              | ↑AEA blood              |
| Glioblastoma                  | ↑AEA glioblastoma       |
| Meninigioma                   | ↑2-AG meningioma        |

Di Marzo et al, 2007, Curr Opin Lipidol
Endocannabinoids and Chronic Pain

- Endocannabinoid system altered in patients with chronic pain
  - Altered signaling
  - Elevated plasma 2-AG
  - Elevated CB1, CB2 mRNA

## Gene polymorphisms of endocannabinoid system in pathologic states

<table>
<thead>
<tr>
<th>Gene</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB1</td>
<td>schizophrenia, Parkinson’s’s addiction (cocaine, alcohol), eating disorders</td>
</tr>
<tr>
<td>CB2</td>
<td>Osteoporosis, autoimmune disorders</td>
</tr>
<tr>
<td>FAAH</td>
<td>addiction, obesity</td>
</tr>
</tbody>
</table>

Di Marzo et al, 2007, Curr Opin Lipidol
Endocannabinoid System

• Over-activity
  – May be associated with obesity, diabetes, cardiovascular disease, liver disease (metabolic syndrome)

• Under-activity (deficiency syndrome)
  – May be associated with migraine, fibromyalgia, irritable bowel syndrome

Robson, 2014, Drug Test Anal
Russo, Cannabis Cannabinoid Res. 2016;1:154
## Therapeutic Potential

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis</td>
<td>Spasticty</td>
</tr>
<tr>
<td>Alzheimer’s</td>
<td>Spasms</td>
</tr>
<tr>
<td>Cerebral ischemia</td>
<td>Seizures</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td>Psychosis</td>
</tr>
<tr>
<td>Huntington’s</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Dementia</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>Tourette’s</td>
<td>Addiction</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>Memory</td>
</tr>
<tr>
<td>Depression</td>
<td>Cognitive disorders</td>
</tr>
</tbody>
</table>

Gowran et al, 2011, CNS Neurosci Ther
Grotenhermen, 2004, Neuro Endocrinol Lett
Therapeutic Potential

Hypothermia
Appetite stimulant
Anti-emetic
Immunomodulation
Hypertension
Obesity
Hyperlipidemia
Decreased insulin resistance
Infertility
Glaucoma
Cancer
Acute pain
Chronic pain
Allergies
Inflammation
Intractable hiccups
Atherosclerosis
Osteoporosis
Sleep
Asthma

Grothenhermen, 2004, Neuro Endocrinol Lett
Goutopoulos et al, 2002, Pharmacol Ther
Clinical Research

- Pain
- Spasticity
- Chemotherapy-induced nausea/vomiting
- Seizures
Cannabinoids for Acute Pain

• Systematic review
  – 7 studies, n=611
• 5 studies: cannabinoids = placebo
• 1 study: cannabinoid superior to placebo
• 1 study: placebo superior to cannabinoid
• 5 studies: cannabinoid side effects > placebo
• Cannabinoids have no role in acute pain

Cannabinoids for Cancer Pain

- Systematic review
  - 8 RCT’s, n=683 (no cannabis)
- Cannabinoids superior to placebo
  - Many studies not statistically significant
  - Nabiximols strongest evidence (3 studies)
  - Use limited by side effects
    - Cognition
    - Sedation
    - Dizziness
- Adjuvant when not relieved with opioids

Cannabinoids for Chronic Pain

• 28 studies
  – 13 nabiximols
  – 4 smoked cannabis
  – 5 nabilone
• 17 high risk of bias
• 30% reduction in pain compared to placebo with nabiximols and smoked cannabis
  OR 1.41 (95%CI, 0.99-2.00)

Whiting et al, 2015, JAMA
Cannabinoids for Chronic Pain

Systematic review – 21 studies

- Design
  - 14 RCT
  - 7 prospective/retrospective cohort studies

- Bias
  - 14 high
  - 6 moderate
  - 1 low

- Funding
  - 17 industry
  - 4 other or unknown

www.health.state.mn.us/topics/cannabis/intractable/medicalcannabisreport.pdf
Cannabinoids for Chronic Pain

• Substances
  – 11 nabiximols
  – 7 nabilone
  – 2 dronabinol
  – 1 oral THC
  – 0 cannabis

• Comparators
  – 19 placebo
  – 2 active treatment

Cannabinoids for Chronic Pain

- Duration (minimum 2 weeks)
  - RCT  2 to 14 weeks
  - Extensions  4 to 124 weeks
  - Cohort  ≥36 months

- Subjects: all adults
  - RCT  median 42 (13 to 339)
  - Extensions  median 104 (28 to 234)
  - Cohort  median 17 (13 to 21)

- Pain
  - 6 MS
  - 10 neuropathic
  - 6 other: fibromyalgia (2), RA (1), mixed (3)

Cannabinoids for Chronic Pain

• Peripheral neuropathic pain
  – Favors nabiximols over placebo (low)

• MS and central neuropathic pain
  – No difference between nabiximols and placebo (low)

• Insufficient evidence for any other substance in any other condition

• Greater risk of any Adverse Event (AE), serious AE, withdrawals due to AE

Cannabis for Chronic Pain

11 systematic reviews, 32 studies

<table>
<thead>
<tr>
<th>Harms</th>
<th>Effect</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis</td>
<td>+ve association</td>
<td>Low</td>
</tr>
<tr>
<td>Mania (BPD)</td>
<td>+ve association</td>
<td>Low</td>
</tr>
<tr>
<td>Cognition</td>
<td>small to moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Suicide</td>
<td>OR=2.56 (CI 1.25-5.27)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>MVA’s</td>
<td>OR=1.35 (CI 1.15-1.61)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Cannabinoids for Neuropathic Pain

• Cochrane review
  – randomized, double-blind controlled trials
    • Minimum 2 weeks, 10 participants
  – 16 studies, n=1750
  – 10 nabiximols
  – 2 nabilone
  – 2 dronabinol
  – 2 cannabis

Mucke et al. Cochrane Database Syst Rev. 2018;3:CD012182
# Cannabinoids for Neuropathic Pain

<table>
<thead>
<tr>
<th>Category</th>
<th>Cann</th>
<th>plnc</th>
<th>RD</th>
<th>95% CI</th>
<th>nnb</th>
<th>Qual</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% ↓</td>
<td>39%</td>
<td>33%</td>
<td>0.09</td>
<td>0.03-0.05</td>
<td>11</td>
<td>Mod</td>
</tr>
<tr>
<td>50% ↓</td>
<td>21%</td>
<td>17%</td>
<td>0.05</td>
<td>0.00-0.03</td>
<td>20</td>
<td>Low</td>
</tr>
<tr>
<td>Neural</td>
<td>10%</td>
<td>5%</td>
<td>0.04</td>
<td>0.02-0.07</td>
<td>25</td>
<td>Mod</td>
</tr>
<tr>
<td>Psych</td>
<td>61%</td>
<td>29%</td>
<td>0.38</td>
<td>0.18-0.58</td>
<td>3</td>
<td>Low</td>
</tr>
<tr>
<td>Serious</td>
<td>17%</td>
<td>5%</td>
<td>0.10</td>
<td>0.06-0.150</td>
<td>10</td>
<td>Low</td>
</tr>
</tbody>
</table>

Mucke et al. Cochrane Database Syst Rev. 2018;3:CD012182
Cannabinoids for Neuropathic Pain

Conclusions

• Harms may outweigh benefits
• Quality of evidence reflects exclusion of patients with addiction and co-morbidities

Mucke et al. Cochrane Database Syst Rev. 2018;3:CD012182
Neuropathic Pain

• Summary of systematic reviews
  – 97 SR, 1429 RCT’s
  – Wide range of neuropathic pain
• Medicinal cannabis not effective for HIV neuropathy (moderate)
• Cannabinoids recommended for central neuropathic pain (moderate)

Cannabinoids for Chronic Pain in Rheumatic Disease

- Systematic review, 4 RCT’s
  - 2 fibromyalgia with nabilone
  - 1 spinal pain with nabilone
  - 1 rheumatoid arthritis with nabiximols
  - No RCT’s for osteoarthritis

- Insufficient evidence for cannabinoids for chronic pain associated with rheumatic diseases

Fitzcharles et al. Schmerz. 2016;30:47
Cannabinoids for Fibromyalgia

- Cochrane review
- 2 studies, n=72
  - Nabilone
- Low tolerability
- No convincing evidence of efficacy

Walitt et al, 2016, Cochrane Review
Cannabinooids for MS Spasticity

• Meta-analysis
  – 16 RCT’s, n=2597
• Decrease in spasticity and spasm
• Not statistically significant
• Adverse effects: dizziness, somnolence, nausea

da Rovare et al. Complement Ther Med. 2017;34:170-185
Cannabinoids for Chemotherapy-Induced Nausea/Vomiting

• 28 studies
  – 14 nabilone
  – 3 dronabinol
  – 1 nabiximols
  – 4 levonantradol
  – 6 THC
• 23 high risk of bias
• Positive response compared to placebo
  – OR 3.82 (95%CI, 1.55-9.42)

Whiting et al, 2015, JAMA
Cannabinoids for Chemotherapy-Induced Nausea/Vomiting

• Cochrane review, 23 studies vs Placebo
  • Absence of vomiting
    – 3 trials, n=168; RR 5.7 (95%CI 2.6 to 12.6) low
  • Absence of nausea and vomiting
    – 3 trials, n=288; RR 2.9 (95%CI 1.8 to 4.7) moderate
  • More chance of withdrawing due to side effects
    – 5 trials, n=664; RR 3.9 (95%CI 1.3 to 12.1) low

Smith et al. Cochrane Database of Systematic Reviews. 2015;11
Cannabinoids for Chemotherapy-Induced Nausea/Vomiting

• Literature review
  – 3 systematic reviews

• Oral cannabinoids (nabilone, dronabinol)
  – Effective compared to placebo
  – No difference compared to prochlorperazine
  – Clinical use limited by adverse effects
    • disorientation, dizziness, euphoria, confusion, drowsiness

Cannabinoids for Appetite Stimulation in HIV

- 4 studies, all dronabinol
- All high risk of bias
- No statistically significant results

Whiting et al, 2015, JAMA
Cannabinoids for Epilepsy

- Cochrane review
- 4 randomized trial reports, all low quality
- Insufficient evidence

Gloss et al. Cochrane Review. 2014
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>

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 cannabinoids

Cannabinoid Side Effects

- Systematic review of side effects with cannabinoids
  - 31 studies, dronabinol, nabiximols
- 4779 adverse effects
  - 96.6% non-serious
  - 196 serious (relapse MS, vomiting, UTI)
  - Rate of non-serious AE greater in subjects taking cannabinoids compared to controls
  - RR 1.86 (95%CI, 1.57–2.21)

- Conclusion: short term cannabinoids increase non-serious adverse effects
  - No increase in serious adverse effects

Wang et al, 2008, CMAJ
## Side Effects of Cannabinoids

<table>
<thead>
<tr>
<th></th>
<th>nnh</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>6</td>
<td>Withdrawal due to AE</td>
<td>14</td>
</tr>
<tr>
<td>CNS effects</td>
<td>6</td>
<td>Sedation</td>
<td>5</td>
</tr>
<tr>
<td>Numbness</td>
<td>4</td>
<td>Hypotension</td>
<td>8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>Psychiatric</td>
<td>9</td>
</tr>
<tr>
<td>Speech disorder</td>
<td>5</td>
<td>Disconnected thoughts</td>
<td>7</td>
</tr>
<tr>
<td>Ataxia</td>
<td>6</td>
<td>Impaired memory</td>
<td>12</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>8</td>
<td>Disorientation</td>
<td>15</td>
</tr>
<tr>
<td>Euphoria</td>
<td>9</td>
<td>Hallucination</td>
<td>17</td>
</tr>
<tr>
<td>Feeling “high”</td>
<td>4</td>
<td>Psychosis</td>
<td>20</td>
</tr>
</tbody>
</table>

Allan et al. Can Fam Phy. 2018:64;111-120
Pharmaceutical Cannabinoids

Low risk of substance use disorder
Summary: Cannabinoids

• Cannabinoids recommended as third line therapy for:
  - Chronic neuropathic pain 14
  - Palliative cancer pain 15
  - Spasticity (MS and spinal cord trauma) 10
  - Chemotherapy-induced nausea/vomiting 3
  - ? Severe, treatment-resistant pediatric seizures?

• Limited by side effects nnh = 6

Allan et al. Can Fam Phy. 2018:64;111-120
Nabiximols Dosing

- Sprays should be separated by 15 minutes
- Held in the mouth for 5 minutes
- Initiate at 1 spray at night
- Increase by no more than 1 spray a day
- Most stabilize at 6 sprays a day (2 tid)
- Maximum 12 sprays a day (4 tid)
- May be used for breakthrough pain
- Dose usually requires no change once stable

Nabilone Dosing

- Initiate at 0.25 to 0.5 mg hs
- Increase dose weekly
- Trial dose 1 mg bid
- Usual maximum dose 2 mg bid
- Maximum dose 3 mg bid
- 8 sprays nabiximols = 2 mg nabilone
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
## Marijuana 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></td>
</tr>
<tr>
<td></td>
<td>60’s and 70’s</td>
<td>1-3% (10 mg/joint)</td>
</tr>
<tr>
<td></td>
<td>80’s and 90’s</td>
<td>6-20% (60-150 mg/joint)</td>
</tr>
<tr>
<td></td>
<td>2017</td>
<td>22-27%</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>70-80%</td>
</tr>
</tbody>
</table>

CBD levels declining

Ashton, 1999, Br J Anaesth
Cannabis Potency

• USA seizures 1995 to 2014
  – Gas chromatography, 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>
<tr>
<td>change</td>
<td>↑ 300%</td>
<td>↓ 50%</td>
<td>↑ 543%</td>
</tr>
</tbody>
</table>

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 with continuous effect on brain

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
Anecdotal Benefits of Smoked Cannabis

• Medical Cannabis and HIV
• n=143
• Improved
  – appetite (97%)
  – muscle pain (94%)
  – nausea (93%)
  – anxiety (93%)
  – nerve pain (90%)
  – depression (86%)
  – paresthesia (85%)
• Reduced memory (47%)

Woolridge et al, 2005, J Pain Symptom Manag
Medicinal Cannabis Trials

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

- Nabiximols: 6000 patient years
- Cannabis: 3 patient years
Medical Cannabis Research

- Neuropathic pain
- Chemotherapy-induced nausea/vomiting
  - No studies
- Multiple Sclerosis spasticity
  - Inadequate data
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
• 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>
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<tbody>
<tr>
<td>placebo</td>
<td>45%</td>
<td>31-60</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2.9%</td>
<td>70%</td>
<td>54-83</td>
<td>.02</td>
<td>4</td>
<td>2.1-25.3</td>
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<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

Cannabis for Neuropathic Pain

• Cochrane review
  – randomized, double-blind controlled trials
    • Minimum 2 weeks, 10 participants
• 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>
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<tr>
<td>↓ cognition</td>
<td>8.32</td>
<td>-0.35</td>
<td>8.67</td>
<td>=0.003</td>
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<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 (3 years)

• 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

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
    • TCA, gabapentinoid, SNRI, opioid, pharmaceutical cannabinoid
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
Seizure disorder
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, planning to become pregnant, or breastfeeding
Under 25

Increased risk of:

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

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

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
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
- Urine drug screens
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, 9 studies
  – observational epidemiology studies with an appropriate control group
  – selected studies that measured recent cannabis use by toxicological analysis or self report
  – 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 and Driving

Advise no driving:

- Four hours after inhalation
- Six hours after oral ingestion
- Eight hours if the patient experiences euphoria
Complications

• Cannabis use disorder
• Hyperemesis syndrome
• Anxiety and mood disorders
• Psychosis
• Cognitive dysfunction
• Cardiovascular disease
• Respiratory disease
• Pregnancy
• Poisoning
Cannabis Use Disorder

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

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
Cannabinoid Hyperemesis

- Chronic, heavy use of cannabis
- Recurrent episodes of severe nausea and intractable vomiting
- Abdominal pain
- Temporary relief of symptoms by taking a hot bath or shower
- Resolution when cannabis use is stopped

Sullivan, 2010, Can J Gastroenterol
Cannabis and Anxiety

• Meta-analysis of prospective longitudinal studies
  – 10 studies, n=58,538
• OR=1.15 (95%CI 1.03 to 1.29)
• High-quality studies (5)
  – OR=1.04 (95%CI 0.91 to 1.19)
• Adjusting for publication bias
  – OR=1.08 (95%CI 0.94 to 1.23)

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 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, 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 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

• Depth of inhalation and length breath held greater than cigarettes
  – carbon monoxide blood levels x 5

• ? Independent risk factor for COPD

• ? Increased risk of lung cancer

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
  - 1 joint a week for 49 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 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 and Pregnancy

• Prospective study
• N=24,874 over 7 year period
• 2.6% prenatal use

<table>
<thead>
<tr>
<th>Outcome</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 2nd 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
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>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rate 95%CI</td>
<td>rate 95%CI</td>
<td>% 95%CI</td>
<td></td>
</tr>
<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>
<td>.02</td>
</tr>
<tr>
<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>
<td>&lt;.001</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>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

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

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

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 potential complications
  – Addiction
  – Anxiety and depression
  – Psychosis
  – Cognitive dysfunction
  – Cardiovascular and respiratory
  – Pregnancy
  – Driving
Summary: Cannabis

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

• Contraindications
  – Substance use disorder (CUD)
  – Age < 25
  – Psychosis (personal or family history)
  – Unstable cardiovascular disease
  – Severe respiratory disease
  – Pregnancy
Summary: Cannabis

• 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