Medical Cannabis & Cannabinoids

Dr. Caroline MacCallum
MD, FRCP (Internal Medicine), B Sc. Pharmacy
Clinical Instructor, Faculty of Medicine, UBC

Email: macallum.caroline@gmail.com
Web: www.drcarolinemaccallum.com

Dept of Internal Medicine, cross appt in Hematology/bone marrow transplant @ VGH
Dept of Internal Medicine @ UBC hospital
Cannabis Authorization & Research @ Greenleaf Medical Clinic

I have the following Relationships with commercial interests:
• Advisory Board: Emerald Health Botanicals, Shoppers Drug Mart, Vitality Biopharma
• CME content: MD Briefcase, Canopy Growth
• Speaker Fees: Canopy Growth, Shoppers Drug Mart
• Other: Medical Director, Greenleaf Medical Clinic

Learning Objectives

1. Endocannabinoid system and cannabis mechanism of action
2. Evidence for medical cannabis, “Indications” and contraindications
3. Cannabinoid products, routes, side effects and monitoring
4. Clarifying common cannabis myths – smoking vs. vaporization, CBD vs. THC, medical vs. recreational cannabis, illegal vs. legal medical cannabis sources in Canada.

Biopsychosocial Impact of Complex disease

Quality of Life
• Physical functioning
• Ability to perform activities of daily living
• Work
• Recreation

Psychological Morbidity
• Depression
• Anxiety, anger
• Sleep disturbances
• Loss of self-esteem

Social Consequences
• Marital/family relations
• Intimacy/sexual activity
• Social isolation

Socioeconomic Consequences
• Healthcare costs
• Disability
• Lost workdays

Morbidity & Mortality of Pain “treatments”

<table>
<thead>
<tr>
<th>Medication</th>
<th>Deaths/Toxicity</th>
<th>Other</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>~36/yr</td>
<td>287 deaths 2005-13</td>
<td>4500 admission in Canada/year</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>16,500 / yr</td>
<td>103,000 hospital admissions/yr in US</td>
<td>Singh 2000 (US stat)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>29,001</td>
<td>T1 = 10:1</td>
<td>US CDC 2013</td>
</tr>
<tr>
<td>Opioids (Rx)</td>
<td>&gt;14,000</td>
<td>T1 = 70:1</td>
<td>US CDC 2014</td>
</tr>
<tr>
<td>Cannabis</td>
<td>LD50 = inhale 1500 lbs in 15 min</td>
<td>T1 = 1000:1</td>
<td>CDC &amp; Health Canada</td>
</tr>
</tbody>
</table>


76 F living independently at home
• RFR: neuropathic pain
• PmHx: DM, HTN, anxiety, OP, OA, DDD
• Rx: metformin, glyburide, ramipril, alendronate, gabapentin, morphine
• Previous Rx: pregabalin, citalopram, venlafaxine, T3, amitriptyline
• Complex Pain Symptoms: pain, nausea, anxiety, insomnia
• ADE: opioid, TCA, gaba = sedation, constipation, dry mouth, urinary retention

Case 1

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Definitions

- **Cannabinoids** are a class of compounds that act on cannabinoid receptors in the human body
- **Endocannabinoids** are cannabinoids that are naturally produced in the body (endogenous)
- **Phytocannabinoids** are cannabinoids produced by the cannabis plant
- **Synthetic cannabinoids** are laboratory-synthesized compounds that bind to cannabinoid receptors

The Endocannabinoid System

- **Lipid signaling system in human body**
- Involved in most physiologic and pathophysiologic processes in the human body including:
  - PAIN
  - Appetite/digestion
  - Sleep/Wake
  - Psychiatric disease
  - Immune function
  - AND many many more....

Distribution of CB1 &2 in body

How Do Cannabinoids work?

Cannabis vs. Rx for Neuropathic Pain

Endocannabinoid Tone

Glia

Descending Inhibitory Pathways

Peripheral Sensitization

Central Sensitization

Ca++:

NE/SHT, enkephalins

Cannabinoids

TCA

5HT/NE reuptake inhibitors

SSRI

Alpha adrenergic agents

Opioids

* Just one MOA

*MacCallum, modified from Beydoun 2003
Phytocannabinoids Basics

- 450 compounds in Cannabis plant
- > 100 Cannabinoids with medical value
  - Nonpsychoactive = CBD (cannabidiol), CBG, CBC etc.
  - Psychoactive = Δ-9-THC (tetrahydrocannabinol)
- Non cannabinoïds (nonpsychoactive & medical value)
  - Terpenes & Flavonoids
- Cannabis species
  - Sativa (energizing) & Indica (relaxing)
- THC/CBD (raw plant) → heat → decarboxylate → THC/ CBD

Cannabis has Multiple Actions

- THC: Analgesic, muscle relaxant, anti anxiety, anti depressant, psychoactive*, antiemetic
- CBD : Anti inflammatory, analgesic, antiemetic, anti anxiety, anti psychotic, anti depressant, may counteract THC and help “reduce the high”
  *CBD + THC = "high" of THC + “entourage effect”
  *Ratio of CBD : THC influences the therapeutic effects.

Cannabis & Polypharmacy Reduction

- CB1 is 10 times more abundant than μ opioid receptors
- Coanalgesic Effects - Cannabinoids exhibit analgesic effects and may potentiate the anti-nociceptive effects of opioids.
- So the same dose of opioids may be more potent. This may make it easier to wean down/off opioids.
- * I provide referred patients with a taper regimen which they can work on with their GP.

Cannabis & Pain

- Can prevent peripheral nociception:
  - Decreasing nociceptor sensitizers
  - Decreasing nociceptor activators
  - Hyperpolarizing nociceptor
- Central analgesia via:
  - Inhibition of GABA, glycine, and glutamate release
  - Blocking NMDA in dorsal horn cell
- Local analgesia via:
  - Inhibition of mast cell function
  - Inflammatory action of PG
  - Substance P

MOA of Cannabis in Pain

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MOA of Cannabis in Pain (cont.)

- CBD
  - Boost natural ECS (↑AEA & 2AG)
  - ↓ inflammatory cytokines TNF and IL6 etc
  - Influence psychoimmunology
  - Stress hormones & HPA axis
  - Decrease anxiety and depression
  - Decrease PTSD (and painful / fearful memory)
  - Action on δ and μ opioid receptors

Cannabinoids & Nociceptor

![](image1)

RCT in Cannabinoids in Pain

<table>
<thead>
<tr>
<th>Pain Category</th>
<th>Nabilone (oral solution) 3.5mg THC + 2.5mg CBD</th>
<th>Cannabis (intranasal spray) 10mg THC, 10mg CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic pain (Wright et al.)</td>
<td>Decreased pain intensity (Wright et al.)</td>
<td>Decreased pain intensity (Wright et al.)</td>
</tr>
<tr>
<td>Fibromyalgia pain (Rahaj et al.)</td>
<td>Decreased pain intensity (Rahaj et al.)</td>
<td>Decreased pain intensity (Rahaj et al.)</td>
</tr>
<tr>
<td>Osteoarthritis pain (Fitzgerald et al.)</td>
<td>Decreased pain intensity (Fitzgerald et al.)</td>
<td>Decreased pain intensity (Fitzgerald et al.)</td>
</tr>
<tr>
<td>Diabetic neuropathy (Thorn et al.)</td>
<td>Decreased pain intensity (Thorn et al.)</td>
<td>Decreased pain intensity (Thorn et al.)</td>
</tr>
<tr>
<td>Cancer pain (Rohal et al.)</td>
<td>Decreased pain intensity (Rohal et al.)</td>
<td>Decreased pain intensity (Rohal et al.)</td>
</tr>
<tr>
<td>Chronic pain + opioids (Nelson et al.)</td>
<td>Decreased pain intensity (Nelson et al.)</td>
<td>Decreased pain intensity (Nelson et al.)</td>
</tr>
<tr>
<td>Oral cancer pain (Hayes et al.)</td>
<td>Decreased pain intensity (Hayes et al.)</td>
<td>Decreased pain intensity (Hayes et al.)</td>
</tr>
<tr>
<td>Cancer pain + opioids (Sau et al.)</td>
<td>Decreased pain intensity (Sau et al.)</td>
<td>Decreased pain intensity (Sau et al.)</td>
</tr>
<tr>
<td>Cancer pain + opioids (Sau et al.)</td>
<td>Decreased pain intensity (Sau et al.)</td>
<td>Decreased pain intensity (Sau et al.)</td>
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<td>Decreased pain intensity (Sau et al.)</td>
<td>Decreased pain intensity (Sau et al.)</td>
</tr>
<tr>
<td>Cancer pain + opioids (Sau et al.)</td>
<td>Decreased pain intensity (Sau et al.)</td>
<td>Decreased pain intensity (Sau et al.)</td>
</tr>
</tbody>
</table>

- DB, placebo controlled, RCT
- NP pain patients on traditional rx
- Vapорized cannabis, 8-12 puffs over 3 h.
- Significant reduction in NP pain (VAS, NP pain scale etc)
  - p<0.0001 at 3h, p=0.0018 at 5h
- Psychoactive effects were minimal
- Low dose = medium dose for pain efficacy ***

Cannabis Guidance Documents (ref)

- Cannabis does not have a DIN and therefore not approved by HC
- This document Reviews safety data and research
- Does not provide day to day practical direction or clinical information on “how to” authorize cannabis

Cannabis “Guidance” Documents (ref)

- I take issue with these topics in the document:
  - Nabilone should be used pre-cannabis
  - Cannabis “should not be used” for:
    - Fibromyalgia, Back Pain, Anxiety, Insomnia
  - “should” use 9% THC or less (based on compass study)
**Potential Therapeutic Uses of Cannabis**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD/ADD</td>
<td>Yes</td>
</tr>
<tr>
<td>Alzheimer’s/Dementia</td>
<td>Yes</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Yes</td>
</tr>
<tr>
<td>Epilepsy/Seizures</td>
<td>Yes</td>
</tr>
<tr>
<td>Arthritis Type</td>
<td>Yes</td>
</tr>
<tr>
<td>Back/Neck Problems</td>
<td>Yes</td>
</tr>
<tr>
<td>Ritalin Linked</td>
<td>Yes</td>
</tr>
<tr>
<td>Head/Pale</td>
<td>Yes</td>
</tr>
<tr>
<td>Hair Loss</td>
<td>Yes</td>
</tr>
<tr>
<td>Stroke</td>
<td>Yes</td>
</tr>
<tr>
<td>Cancer</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic Pain/Neural Pain</td>
<td>Yes</td>
</tr>
<tr>
<td>Other</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Future uses: DM, CAD, NASH, COPD, asthma, psoriasis, autism, pyoderma gangrenosum

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**CFPC Cannabis Guidance Document**

“Relative Contraindications”

Cannabis is generally not appropriate for patients who:

- a. are under the age of 25
- b. have a personal history or strong family history of psychosis
- c. have a current or past cannabis use disorder
- d. have an active substance use disorder
- e. have cardiovascular (angina, peripheral vascular disease, cerebrovascular disease, arrhythmia) or respiratory disease
- f. are pregnant, planning to become pregnant or are breastfeeding

*Adverse events are due to THC and are dose dependent. I have successfully used cannabis in these patients by using CBD only or low dose THC

**Resp concern is due to smoking cannabis (not oil/vap)

CFPC = College of Family Physicians of Canada

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**Natural vs. Synthetic Cannabinoids (ref)**

<table>
<thead>
<tr>
<th>Natural Cannabis</th>
<th>Synthetic (ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+Adverse events are due to THC and are dose dependent. I have successfully used cannabis in these patients by using CBD only or low dose THC</td>
<td></td>
</tr>
</tbody>
</table>

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**Source of Cannabis (in Canada)**

<table>
<thead>
<tr>
<th>Issue</th>
<th>LP</th>
<th>Dispensary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Canada Regulated</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>Legal Cannabis</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>“Medical Card” (does not imply patient is “legal”)</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Strict testing for metal, toxins, pesticides, fungus, contaminants etc.</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>Consistency of THC &amp; CBD %</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>Authorized by MD</td>
<td>✔ &amp; ✗</td>
<td></td>
</tr>
<tr>
<td>Onsite distribution</td>
<td>✗</td>
<td></td>
</tr>
</tbody>
</table>

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**Routes of Administration**

<table>
<thead>
<tr>
<th>Route</th>
<th>Onset (min)</th>
<th>Duration (h)</th>
<th>Pro</th>
<th>Con</th>
<th>Coa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>5-10</td>
<td>6-8</td>
<td>Rapid, advantage for acute or episodic symptoms (common pain)</td>
<td>Less odour, convenient and discreet, advantage for chronic disease symptoms</td>
<td>Easier to control, no experience required, and the product is more economical</td>
</tr>
<tr>
<td>Oromucosal</td>
<td>15-45</td>
<td>6-8</td>
<td>Pharmacological equivalent (nabiximols) available, with documented efficacy and safety</td>
<td>Less systemic effect, good for localized symptoms</td>
<td>Expensive, complicated to use, and the product is more expensive</td>
</tr>
<tr>
<td>Topical</td>
<td>Variable</td>
<td>Variable</td>
<td>Topical effective, advantage for localized symptoms</td>
<td>Less odour, convenient and discreet, advantage for chronic disease symptoms</td>
<td>Easier to control, no experience required, and the product is more economical</td>
</tr>
</tbody>
</table>

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**Vaporizing vs. Smoking**

- Smoking @ 600-900C ➔ CO + carcinogens
- Vap @ 180-200C ➔ little, if any CO (Abrams et al 2007)
- Vap = more efficient, $ saving (30-50% less) & safer
- So far, 2 vaporizers = medical devices by HC
- 1 cannabis cig = x4 tar of nicotine cig. Also many patients mix tobacco with cannabis.

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**Table created by Dr. MacCallum**

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* Flower/oil are legal herbal sources of cannabis in canada

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Dosing

• Medical goal = lowest dose of THC for symptom control and functional improvement
  • “Start low, go slow and stay low.”
  • THC start = 2.5 mg → 5 mg → 7.5 mg → 10 mg
  • Self titrate to lowest THC dose (max benefit & min ADE)
  • No real dosing guidelines for CBD
  • Avg dose cannabis = 1-3 g/day (5% use > 3 g / day - Ware et al)
  • Tolerance to adverse effects but NOT to benefit


Side Effects (2° THC)

Metabolism & Drug Interactions (ref)

• Most DI are associated with concurrent use of other CNS depressants
  • Clinically significant drug interactions are unlikely
    • Exception - ↑ clobazam levels with very high dose CBD
    • “In clinical trials where SATIVEX® (CBD 2.5mg/THC 2.7mg per spray) has been taken concomitantly with other drugs metabolized by the CYP450 enzyme system, no clinically apparent drug-drug interactions have been seen in these trials at clinical doses.”
    • SATIVEX has been studied for > 10 years with 6000 patient year data.
    • Extensive DI studies have not been done. Existing studies have not demonstrated toxicity/ loss of effect of concomitant medications, but still theoretically possible (Health Canada 2013)

Animal / Invitro Studies (ref)

• THC is oxidized by (CYP) 2C9, 2C19, and 3A4
  • ↑ THC – with inhibitors (fluoxetine, omeprazole, macrolides, ketoconazole, diltiazem, verapamil, HIV proteases, amiodarone)
  • ↓ THC - 2C9, 3A4 inducers (rifampicin, phenytoin, St. John’s Wort)
• THC inhibits CYP 1A1, 1A2, 1B1
  • ↑ amitriptyline, theophylline, granisetron, flutamide

Monitoring

• Response/efficacy
• Strains/dose (? ↑↓ % CBD/THC)
• Route (change to oil?)
• Potential drug interactions
• Review meds & consider a slow taper (opioids, benzo etc)
• Repeat anxiety GAD-7, depression PHQ-9, pain BPI scale, Q of L and functional improvement
Driving Considerations

- Cannabis intoxication (THC) increases the risk of collision related morbidity and mortality up to 3 fold
- Similar to caution with other medications which impair judgment including: opioids, muscle relaxants, alcohol
- If using cannabis daily, THC tolerance will develop and there may be minimal impairment (similar to tolerance to prescription opioids)
- BOTTOM LINE: If impaired DO NOT drive / do safety sensitive job

Cannabis Rx

1. Focus on Sleep – THC helps with pain, anxiety and insomnia. If sleep improves, so will daytime pain, anxiety, mood etc.
   - Strategy for bedtime dosing:
     - THC Oil for ingestion for “long acting” relief
     - THC Vaporization for “short acting” relief
     - Use “sedating” (indica) THC

2. Daytime - CBD oil to minimize impairment
3. “Energizing” (sativa) vaporization “short acting” for severe daytime pain (counsel on driving / potential impairment).
4. Follow up visit: Slow Taper off opioids/Rx if appropriate.

Treatment Approach to Chronic Pain

1. Multiple concurrent diseases
2. Symptom clusters (sleep, mood, anxiety, nausea etc)
3. Multiple prescription Rx failures
4. Reduce Adverse Drug Events
5. Reduce Polypharmacy
6. Co-analgesia Effect of Cannabis & Opioid
7. Help with withdrawal SE when tapering opioids, SSRI, TCA etc
8. > 20 Mechanism of Action for Pain. Can help multiple pain generators ie. neuropathic, nociceptive, mechanical

Take Home Points

- Vaporizing ≠ Smoking
- Lowest THC dose = ☝️ benefit & ◀️ ADE
- CBD & Terpenes = medical benefit & NOT psychotropic
- CBD + THC = ☝️ “high” of THC (+ “entourage effect”)
- Recreational users ≠ Medical users (symptom control vs. euphoria)
- Safer than opioids (> 100,000 deaths vs. 0 since 2000)
- Driving issues = similar to opioids
- LP = consistent, safe and leg medicinal cannabis
Education on Opioids Tapering

No more than 10% reduction every 1-2 week
May require 5% reduction every 1-2 week when at lower doses
Opioid taper WILL result in withdrawal pain with EACH reduction in dose (each “cycle” of withdrawal will resolve within 5 days).

For unpleasant withdrawal symptoms, consider:
- Clonidine/propranolol (anxiety, tremors, palpitations)
- Loperamide (diarrhea)
- Oxybutynin (sweating)
- Antihistamines (runny eye/nose)
- Cannabis (has co-analgesic/synergistic effects when used with opioids which can make it even more favourable when tapering off opioids specifically)

UBC “This Changed My Practice”

Books for Patients

The Anxiety and Phobia workbook, Edmund J Bourne (~20$)
The Chronic Pain Care Workbook, Michael J Lewandowski (~20$)
Holistic Pain Relief Dr. Heather Tok: Integrative pain medicine
Living Well with Pain and Illness: Vijayaloka Burch
How to be Sick: A Buddhist Inspired Guide for the Chronically Ill and their Caregivers (Tori Bernhard)
Meditation Exercises to Enlighten the Mind and Heal the Body: Tulku Thondup
Jon Kabat-Zinn is one of the better known authors on mindfulness
Neil Pearson's "Understand Pain, Live Well Again" book
http://www.painsense.ca/pain-management-products/
Explain Pain by Moseley is always a good choice too, it's a classic
http://www.amazon.ca/Explain-Pain-Teo-V-Butler/dp/B00745Y0X4

Handouts For Patients

• Pain Toolkit
https://www.painbc.ca/sites/default/files/PainBC-PainToolbox-2016-Digital.pdf
• CSS handout
• Opioid withdrawal

Cannabis Evidence (ref)

• Pain Toolkit
https://www.painbc.ca/sites/default/files/PainBC-PainToolbox-2016-Digital.pdf
• CSS handout
• Opioid withdrawal

Extra Cannabis Slides

Cannabis Mechanism of Action in Chronic Pain

Prevention peripheral nociception
• Decreasing nociceptor sensitiveness
• Decreasing nociceptor activation
• Hyperpolarizing nociceptor

Central analgesia via
• Inhibition of GABA, glycine, and glutamate release
• Blocking NMDA in dorsal horn cell

Local analgesia via
• Inhibition of mast cell function

CBD
• Boost natural ECS (increase AEA & 2AG)
• Decrease inflammatory cytokines TNF and IL6, etc.

Influence psychoneuroimmunology
• Stress hormones & HPA axis
• Decrease anxiety and depression
• Decrease PTSD (and painful/fearful memory)
• Action on δ and μ opioid receptors

**Conditions and Cannabis Evidence (ref)**

<table>
<thead>
<tr>
<th>Title</th>
<th>Reference</th>
<th>Number of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>A greater average number of patients showing a complete nausea and vomiting response in patients treated with nabiximols or nabilone.</td>
<td><a href="#">Novotna et al. 2011</a></td>
<td>337/144/58</td>
</tr>
<tr>
<td>Multicenter, Double-blind, Placebo-controlled trial of Sativex, a cannabinoid extract in patients with symptoms of spasticity due to multiple sclerosis</td>
<td><a href="#">Ellis et al. 2009</a></td>
<td>337</td>
</tr>
<tr>
<td>A greater average reduction in numerical rating scale pain assessment (on a 0-10 pain scale, weighted mean difference [WMD], −0.46 [95% CI, −0.80 to −0.11] vs placebo)</td>
<td><a href="#">Langford et al. 2013</a></td>
<td>337</td>
</tr>
<tr>
<td>An average reduction in the Ashworth spasticity scale (WMD, −0.36 [95% CI, −0.69 to −0.05]) vs placebo</td>
<td><a href="#">Langford et al. 2013</a></td>
<td>337</td>
</tr>
<tr>
<td>Higher risk of adverse effects</td>
<td><a href="#">Grotenhermen 2010</a></td>
<td>2017-11-17</td>
</tr>
<tr>
<td>Cannabis “fine print”</td>
<td></td>
<td>2017-11-17</td>
</tr>
<tr>
<td><strong>Cost</strong>: minimum $5/g x 1g/d = 150$/mo.</td>
<td></td>
<td>2017-11-17</td>
</tr>
<tr>
<td>Compassionate pricing for patients on disability or &lt;30K/yr. Usually 6-8/g.</td>
<td></td>
<td>2017-11-17</td>
</tr>
<tr>
<td><strong>Lock box</strong>: Patient has been advised to use a locked box to so store his cannabis if there are children visiting/living in the home.</td>
<td></td>
<td>2017-11-17</td>
</tr>
<tr>
<td><strong>Safety</strong>: safety sensitive occupation &amp; activities, as well as implications of work urine drug screening were discussed.</td>
<td></td>
<td>2017-11-17</td>
</tr>
<tr>
<td>Urine drug screen: can be + for 3 wk after THC use.</td>
<td></td>
<td>2017-11-17</td>
</tr>
</tbody>
</table>

**Neutropenic / Immunosuppressed Patients**

- **Dried Product/bud**: get from an LP which uses GAMMA RADIATION to kill fungus/bacterial. So that these contaminants are not inhaled.

- **Oil**: the extraction process of CBD/THC from dried product into oil should kill fungus/bacteria, therefore gamma radiation is not as big an issue.
Cannabis and Youth

Increased risk of addiction
In those at risk, younger age of first cannabis use is associated with younger age of schizophrenia and bipolar disorder and worse outcomes
Regular users < 18 years old have increased risk of persistent cognitive effects
Regular use in youth associated with increased social dysfunction, anxiety and depression

Is Cannabis Addictive?

Comparing Dangers of Popular Drugs
(Lower score indicates less serious effect)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Experience</th>
<th>Withdrawal</th>
<th>Reinforcement</th>
<th>Intoxication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Marijuana</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cannabis</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Schizophrenia

There is evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users. (Abrams 2017)

"...an increased familial morbid risk for schizophrenia may be the underlying basis for schizophrenia in cannabis users and not cannabis use by itself." (Proal et al. 2014)

"...cannabis does not induce schizophrenia in non-vulnerable individuals." (Hill 2015)

In individuals with schizophrenia and other psychoses, a history of cannabis use may be linked to better performance on learning and memory tasks. (Abrams 2017)

Cannabinoid–Opioid Interaction in Chronic Pain

• Chronic pain – MSK, post traumatic, arthritis, cancer, FM, migraine, MS, sickle cell, thoracic outlet syndrome
• 21 Cannabis non-naïve subjects on LA morphine/oxycodone
• 5 day study = vaporized cannabis in the PM day 1, TID on days 2–4, and in the AM of day 5
• Statistically significant 27% [95% CI 9 – 46] ↓ in pain score
• No significant effect on opiate metabolism
• Limitations: sm size, short duration, not randomized, No placebo
First placebo controlled, DB, RCT in RA

- 1 spray = THC 2.7% & 2.5% CBD (=CBDM)
- CBM produced statistically significant improvement in pain on movement, pain at rest, quality of sleep, DAS28, and SF-MPQ pain
- Majority of AE were mild/mod
- No withdrawal/serious AE

RCT, DB, placebo controlled crossover design

- 37 cannabis naïve or exposed MS patients with moderate spasticity
- Avg of 4 puffs of 4% THC vs. placebo cigarettes
- Primary outcome = Significantly improved spasticity (p<0.001)
- Also significantly improved pain (P=0.008), significant reduction in cognitive function (p=0.003)
- No significant change in physical function

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