TODAY’S AGENDA

Cannabinoids & The Endocannabinoid System

ENDOCANNABINOIDS
(Produced and produced in the human body)

Anandamide
2-AG

PHYTOCANNABINOIDS
(Found and produced in plants)

9 THC
CBD

Cannabinoids & The Endocannabinoid System

Anandamide

9 THC

PLANT CHEMICAL

HUMAN CHEMICAL

The Endocannabinoid System (ECS)

CB1 & CB2 RECEPTORS

CB1 RECEPTORS

Cannabinoid Effects on CB1 Receptors
- Decreased pain (analgesia)
- Decreased nausea and vomiting
- Increased appetite
- Increased muscle control
- Sleep aid
- Memory suppressant
- Anti-prolific

CB2 RECEPTORS

Cannabinoid Effects on CB2 Receptors
- Anti-inflammatory
- Increases immune function
- Decreased pain (analgesia)
- Anti-prolific

Phytocannabinoids

ACTIVE CANNABIS COMPONENTS

Some Effects of THC:
- Decrease pain
- Stimulate appetite
- Analgesic
- Anti-emetic
- Sleep aid
- Psychotropic

Some Effects of CBD:
- Mitigation of psychotropic effects of THC
- Analgesic
- Anti-inflammatory
- Anti-epileptic
- Anxiolytic

TARGETS PRIMARILY CB2 RECEPTORS

Cannabinoid

CB2 Receptor
Entourage Effect
From the "Whole Plant"

• Terpenes
• Terpenoids:
  - Responsible for scent as well as have a broad Spectrum of action

• Limonene:
  - Citrus - Gastric Reflux, Anti-fungal, Anti-depressant, Anti-anxiety

• α-Pinene:
  - Pine - Anti-inflammatory, Bronchodilator, Aiding in Memory

• β-Myrcene:
  - Mango and more - Anti-inflammatory, Analgesic, Anti-tumor, Muscle Relaxant

• Linalool:
  - Lavender - Anti-Anxiety, Sedative (sleep-aid), Analgesic, Anti-convulsant

• Caryophyllene Oxide:
  - Cloves - Anti-Fungus, Anti-Tumor, Anti-Oxidant, Improved uptake of CBD/CBC

• "Entourage Effect"
• 500 Different Chemical Compounds
• All of these compounds work together


TODAY’S AGENDA

Approved Conditions

Intractable Pain
Cancer (pain, N/V, cachexia)
HIV/AIDS
Seizures

Obstructive Sleep Apnea
Autism
PTSD
Tourette’s Syndrome

Glaucoma
ALS
Muscle Spasms
Inflammatory Bowel Disease

Terminal Illness
Alzheimer’s Disease*

*Summer 2019

Approved Indications in Minnesota
What is "Terminal Illness"?

As defined by the state of Minnesota, terminal illness is an illness with a probable life expectancy of less than one year. To qualify for the program, the illness or its treatment produces one or more of the following: severe or chronic pain; nausea or severe vomiting; or Cachexia or severe wasting.

What is "Intractable Pain"?

As defined by the state of Minnesota, intractable pain is a pain state where the cause of pain cannot be removed or otherwise treated. It is a state in which no relief or cure of the cause of pain is possible.

Primary causes of such pain include, but are not limited to:

<table>
<thead>
<tr>
<th>1. Arthritis: rheumatoid</th>
<th>12. Lupus</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Complex Regional Pain Syndrome</td>
<td>15. Myelopathy</td>
</tr>
<tr>
<td>5. Crohn Disease</td>
<td>16. Myasthenia</td>
</tr>
<tr>
<td>6. Disc (ventral) herniation</td>
<td>17. Neck pain</td>
</tr>
<tr>
<td>11. Low back-pain</td>
<td>22. Parkinson's</td>
</tr>
<tr>
<td>23. Phantom limb pain</td>
<td>24. Post-herpetic pain</td>
</tr>
<tr>
<td>27. Spinal cord injury</td>
<td>28. Spinal stenosis</td>
</tr>
<tr>
<td>29. Trauma (including vertebral compression fracture)</td>
<td>30. Trigeminal neuralgia</td>
</tr>
<tr>
<td>31. Vascular disease</td>
<td>32. OTHER</td>
</tr>
</tbody>
</table>

TODAY’S AGENDA

Cannabinoids & The Endocannabinoid System

Minnesota Medical Cannabidiol Program

Approved Conditions

Research

Questions
Clinical Research: Limitations

- Regulatory barriers
- Heterogeneity of cannabinoids
- NIDA supply of cannabis

The Health Effects of Cannabis & Cannabinoids: The Current State of Evidence and Recommendations for Research

Cannabinoids & Pain
- Identified five good- to fair- quality systematic reviews and two additional studies.
- Conclusions from all were consistent and found moderate benefit on pain.
- The most rigorous review (Whiting, 2015) found that use of plant-derived cannabinoids increase odds of improvement in pain by 40%.
- Studies conflict as to whether there is a dose dependent effect.

Conclusion: “There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.”

Other Findings

Substantial or Conclusive Evidence
- MS Associated Muscle Spasms
- Chemotherapy Associated Nausea and Vomiting

Moderate/Limited Evidence
- Sleep improvements in patients with OSA, pain, MS, fibromyalgia
- Appetite increase in HIV/AIDS
- Anxiety reduction with CBD for social anxiety
### Uses in Palliative Care

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Formulation</th>
<th>Delivery Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>Higher THC</td>
<td>Inhaled</td>
</tr>
<tr>
<td>Pain</td>
<td>Higher THC  or CBD:THC 1:1</td>
<td>Persistent Pain: Oral Breakthrough Pain: Inhaled or Sublingual Spray</td>
</tr>
<tr>
<td>Appetite Stimulation</td>
<td>Higher THC</td>
<td>Any</td>
</tr>
<tr>
<td>Sleep Disturbances</td>
<td>Higher THC  or CBD:THC 1:1</td>
<td>Sleep Initiation: Inhaled Sleep Maintenance: Oral</td>
</tr>
</tbody>
</table>

### Cannabis in End-of-Life Care: Examining Attitudes and Practices of Palliative Care Providers

**Compared to current treatments, how does cannabis compare for the treatment of the following.**

- Nausea & Vomiting
- Pain
- Appetite Stimulation
- Sleep Disturbances

**How do the side-effects of cannabis compare to current treatments for the treatment of the following.**

- Nausea & Vomiting
- Pain
- Appetite Stimulation
- Sleep Disturbances

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**TODAY’S AGENDA**

- Cannabinoids & The Endocannabinoid System
- Minnesota Medical Cannabis Program
- Approved Conditions
- Questions

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Top Ten Misconceptions About the MN Medical Cannabis Program

- Doctors must “prescribe” cannabis.
- Qualified patients get a “medical marijuana card”.
- Once a provider has certified a patient, obligations in the program cease.
- You can avoid any potential malpractice liability by having your patient sign a waiver.
- The typical cannabis patient is a twenty-something gamer eating chips in the basement.
- Cannabis under Minnesota’s restrictive program is too expensive.
- Cannabis works by getting people “high” so they forget about their symptoms.
- Many patients can’t tolerate Medical Cannabis due to side effects.
- The petition process for adding new qualifying conditions is unscientific.
- It is only a matter of time until MN goes “recreational”.

Doctors Must “Prescribe” Cannabis — FALSE!

- Providers do not prescribe Cannabis of any kind.
- They certify that patients have one of the current 14 “qualifying conditions”.
- Physicians, advanced practice nurses, and physicians assistants may certify patients.
- A Licensed Pharmacist will incorporate the qualifying condition, other medical conditions, and medications to determine the proper form, dose and frequency of Medical Cannabis.

Number of Participating Health Care Practitioners as of 12/31/18
Certified Patients Get a "Marijuana Card" – FALSE!

- Minnesota residents that have a qualifying condition can pay a fee ($50-200 annually) to be entered in the State Registry.
- They are assigned a unique identifying number, go through a detailed background check, and are then sent an email notifying them of their successful entry into the program.
- This process can take up to a month.
- Only then can they visit a Patient Cannabis Center to meet with a pharmacist and be dispensed medical cannabis.

### Table: Breakdown of Registered Health Care Practitioners by Type December 31, 2018

<table>
<thead>
<tr>
<th>Healthcare Practitioner Type</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td>1061 (75%)</td>
</tr>
<tr>
<td>Physician Assistant</td>
<td>104 (7%)</td>
</tr>
<tr>
<td>Advanced Practice RN</td>
<td>250 (18%)</td>
</tr>
<tr>
<td>Total</td>
<td>1,415</td>
</tr>
</tbody>
</table>

Figure 3. Breakdown of active patients by fee type (reduced vs. full fee) and types of government assistance for reduced fees, as of December 31, 2018.
Once a Provider has Certified a Patient, Obligations in the Program Cease -- FALSE!

- You must develop an ongoing plan of care for your patient as the primary practitioner responsible for the care and treatment of the qualifying condition.
- You must monitor the patient for any serious adverse side effects.
- There are also requirements for completing periodic surveys to the Minnesota Office of Medical Cannabis which are then compiled and released as observational data.
- Patients need annual recertification that the qualifying condition continues.
- You can also access your patient’s dosing regimen through the OMC website and send messages to the pharmacists who make recommendations.
- Billing and coding—qualifying condition, not cannabis!

You Should Avoid any Potential Malpractice Liability by Having your Patient Sign a Waiver -- FALSE!

- First, cannabis is accepted medical therapy for patients who have a qualifying condition; regular medical malpractice coverage will apply.
- Second, the key is to have a conversation with your patient to assess the risks and benefits of cannabis therapy, just as one might for the use of opioids, long-term anticoagulation, or chemotherapy.
- You cannot “waive” your obligation to meet the standard of care regarding the use of medical cannabis.
- This presupposes some practitioner knowledge, especially potential drug-drug interactions!
The Typical Cannabis Patient is a 25 YO Male Eating Chips in the Basement -- FALSE!

![Graph showing breakdown of active patients]

<table>
<thead>
<tr>
<th>Qualifying Condition</th>
<th>Patients Certified: N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaucoma</td>
<td>110 (1%)</td>
</tr>
<tr>
<td>IHSS</td>
<td>98 (3%)</td>
</tr>
<tr>
<td>Tourette Syndrome</td>
<td>122 (1%)</td>
</tr>
<tr>
<td>ALS</td>
<td>32 (&lt;1%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>610 (4%)</td>
</tr>
<tr>
<td>Severe and Persistent Muscle Spasticity</td>
<td>1,621 (7%)</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease, Including Crohn's Disease</td>
<td>407 (2%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1,200 (9%)</td>
</tr>
<tr>
<td>Terminal Illness</td>
<td>157 (1%)</td>
</tr>
<tr>
<td>Intractable Pain</td>
<td>9,267 (64%)</td>
</tr>
<tr>
<td>Post-Traumatic Stress Disorder</td>
<td>2,223 (14%)</td>
</tr>
<tr>
<td>Autism Spectrum Disorder</td>
<td>65 (7%)</td>
</tr>
<tr>
<td>Obstructive Sleep Apnea</td>
<td>445 (3%)</td>
</tr>
<tr>
<td>Total</td>
<td>14,481</td>
</tr>
</tbody>
</table>

Number of active MN patients
as of 12/31/18

![Graph showing trend of active patients]
Cannabis Under Minnesota’s Restrictive Program is Too Expensive – WELL, MAYBE!

- Insurance does not cover the cost.
- Some workers comp carriers are beginning to reimburse for it.
- Average patient pays about $200/month, although some pay much more.
- Minnesota allows only highly-processed cannabis formulations—NO LEAF—the most restrictive of the 33 state programs.
- Third party lab testing for biocontaminants and heavy metals.
- Those who wished to consume leaf could conceivably pay half current prices, were it allowed.

Cannabis works by getting people “high” so they forget about their symptoms -- FALSE!

- Products are “strain-independent”.
- Focused on precise formulations of the two main cannabinoids in varying ratios.
- Many patients rely on high CBD ratio products with little chance of inducing psychoactive effects.
- Even for the high THC compounds, evidence shows that even subtherapeutic doses act synergistically with other medications to increase safety and continue effectiveness.
- “Start Low and Go Slow”.

Minnesota Medical Solutions Medications
Minnesota Medical Solutions

**DRUG DELIVERY METHODS**

- Capsules
- Tablets
- Tinctures & Oils

LeafLine Labs Medications

Available Forms:
- Oils for vaporization,
- Sublingual
- Tinctures & sprays,
- Oral suspensions,
- Capsules and topicals

- Tangerine (THC : CBD)
- Heather (THC : CBD)
- Cobalt (THC : CBD)

Minnesota Patterns of Use

- Products for inhalation (vaporized oil) accounted for 54% of products purchased.
- Products for enteral administration (swallowed – capsules and oral solutions) accounted for 39%.
- When all routes of administration are combined, Very High THC:CBD products accounted for 57% of all product purchases.
- Balanced products (33%), High THC:CBD products (6%), High CBD:THC products (4%), and Very High CBD:THC (<1%).
Patient Reported Benefits

- The benefits extended beyond reduction in symptom severity, though that was the benefit mentioned most often.
- The benefit described second most often was improved sleep (27%).
- In some cases improved sleep, reduction of other pain medications and their side effects, decreased anxiety, improved mobility and function, and other quality of life factors were cited as being the most important benefit.
- The pattern of described benefits was similar in the patient and the health care practitioner survey results.

Effect on Other Medications

- A large proportion (58%) of patients on other pain medications when they started taking medical cannabis were able to reduce their use of these meds according to health care practitioner survey results.
- Opioid medications were reduced for 38% of patients (nearly 60% of these reduced at least one opioid by ≥50%), benzodiazepines were reduced for 3%, and other pain medications (e.g., gabapentin, amitriptyline) were reduced for 22%.
Many patients can’t tolerate Medical Cannabis due to side effects — FALSE!

- The safety profile of medical cannabis in MN is quite favorable.
- The vast majority (approximately 90%) are mild to moderate in severity.
- In a 2016 OMC Report on Intractable Pain, an assessment of the 75 patients reporting severe adverse events (“interrupts usual daily activities”) found no apparent pattern in age, primary cause of pain, or type of medical cannabis product used.
- None of the “serious adverse events” required ER visit or hospitalization.
- Monthly reporting is required by the State (SAFETYCALL).

The Petition Process for adding new conditions is Unscientific — FALSE!

- Every Year a two-month period from June 1 – July 31 is available for petitions to the Department of Health to add qualifying conditions and new delivery methods.
- A citizen review panel holds hearings and the OMC develops detailed issue briefs outlining the state of existing research.
- The Commissioner of Health makes decisions that are then effective the following summer.
- These decisions are based on existing science, but also take into account compassionate care.
Some Previously denied MN Conditions

- Anxiety
- Parkinson’s
- Arthritis
- Depression
- Diabetes
- Insomnia
- Schizophrenia
- Panic Disorder
- Traumatic Brain Injury
- Opioid Use Disorder

It is Only a Matter of Time until MN Goes “Recreational” — FALSE!

- HF 766 Rep. Edelson Bill—Modifications to the current Medical Cannabis Program
- HF 717 Rep. Mariani Bill—Establish a task force to evaluate the pros and cons of legalization in Minnesota
- HF 420 Rep. Freiberg Bill—Legalization bill (Note: Minnesota does not allow citizen initiated ballot measures)

Future Legislation?

- Next Session (2020) look for more efforts to bring down costs, which could include the addition of vaporized “flower” as an allowable form of Medical Cannabis.
- Tighter regulation of rampant, untested CBD products.
- IMO, Legalization will not have a chance unless and until the Minnesota Senate were to flip to Democrat.
- Unknown what effect that might have on the patients in the existing Medical Cannabis program.
Summary

• Cannabis, as adjunctive therapy, is effective across a range of medical conditions.
• The science of the human endocannabinoid system explains these effects.
• Practitioners need to be educated about Medical Cannabis—CME, e.g., OMC website.
• Patients do not have to “get high” to get benefit.
• Cannabis is safe, has a low potential for abuse, and can make use of other potentially deadly medications safer.
• MN Program is effective but narrow and expensive.
• Efforts to expand and improve the Program are underway; near-term legislative improvements will be incremental.