BUSINESS INSURANCE®

CANNABIS & HEMP CONFERENCE

OCTOBER 24-25, 2019 | MARRIOTT MARQUIS | NEW YORK CITY

THE SCIENCE OF MEDICAL CANNABIS

Jeremy Riggle, Ph.D.
Chief Scientist
Mary's Medicinals and Mary's Nutritionals
Denver, CO
jeremy@marysmedicinals.com

“25% of all western drugs come from ~120 plant species; 80% of the worlds population is dependent on medicinal plants for primary health care.”

Prof. R. Verpoorte, University of Leiden

About cannabis:

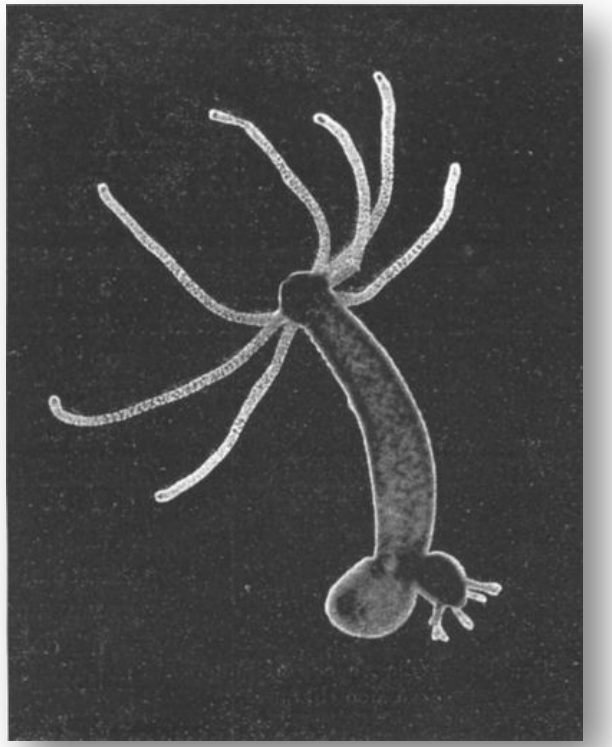
"[...] most useful plant on Earth. No other single plant contains as wide a range of medically active herbal constituents."

Dr. Ethan Russo, Neurologist, Botanist and Cannabis Expert – Cannabinoid Research Institute

100+ phytocannabinoids - *we know a bit about* ***2***;
400+ non-cannabinoid constituents

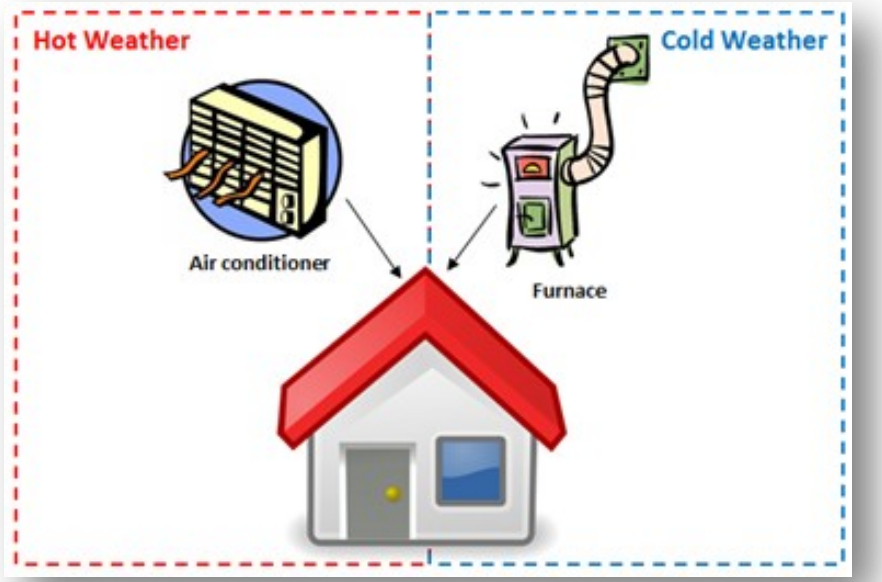
Why are cannabinoids so diverse in terms of potential indications…?

- Regulation of feeding was believed to be the initial function of the ECS in primitive organisms.
- De Petrocellis (1999) showed that in the Hydra, the endocannabinoid anandamide inhibited the feeding response by accelerating mouth closure.
- This system has been found in fossils 500 million years old.
- In more complex organisms (*e.g.* humans) it is thought that the ECS's function evolved into controlling homeostasis.



Homeostasis

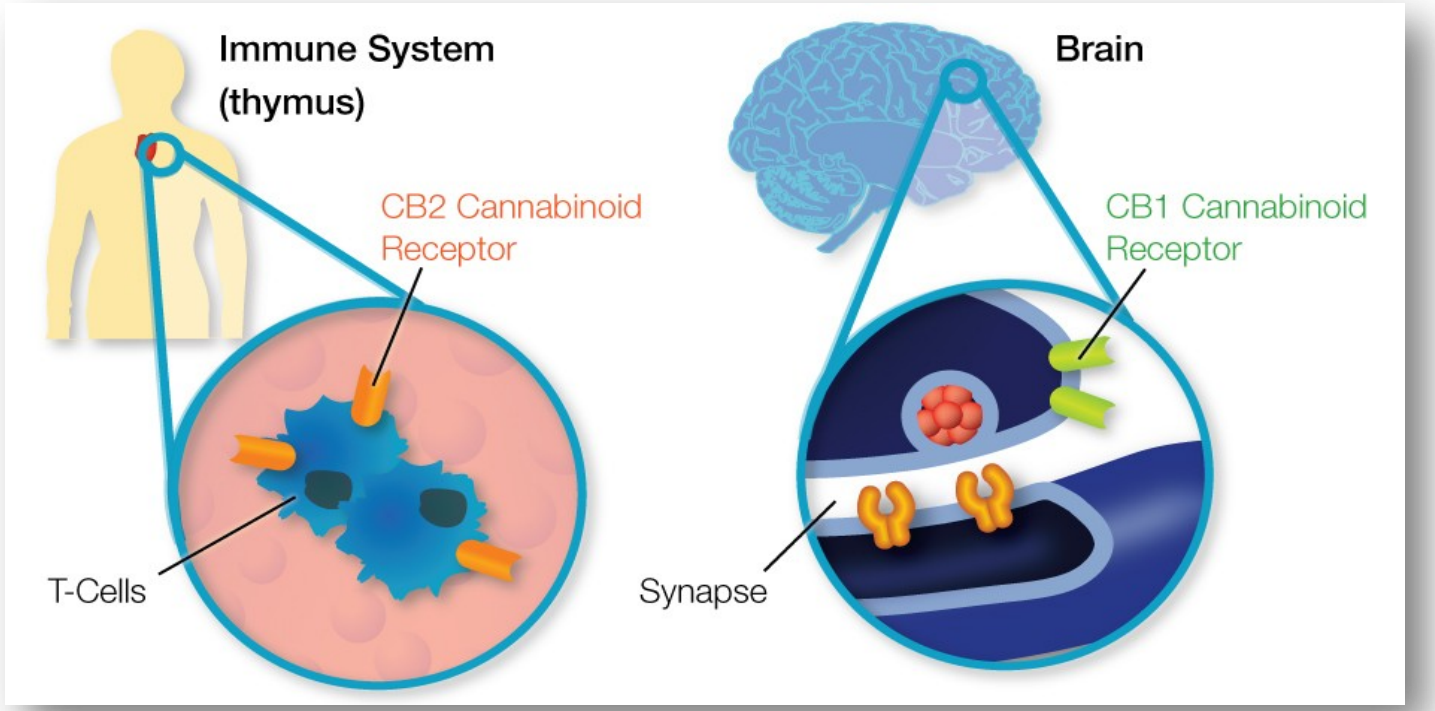
- Refers to the ability of an organism to maintain steady or stable internal condition in spite of external changes.
- Essentially a balancing act at the cellular level that allows cells to function normally despite extracellular conditions.
- *e.g.* internal body temperature.



The ECS includes many elements…

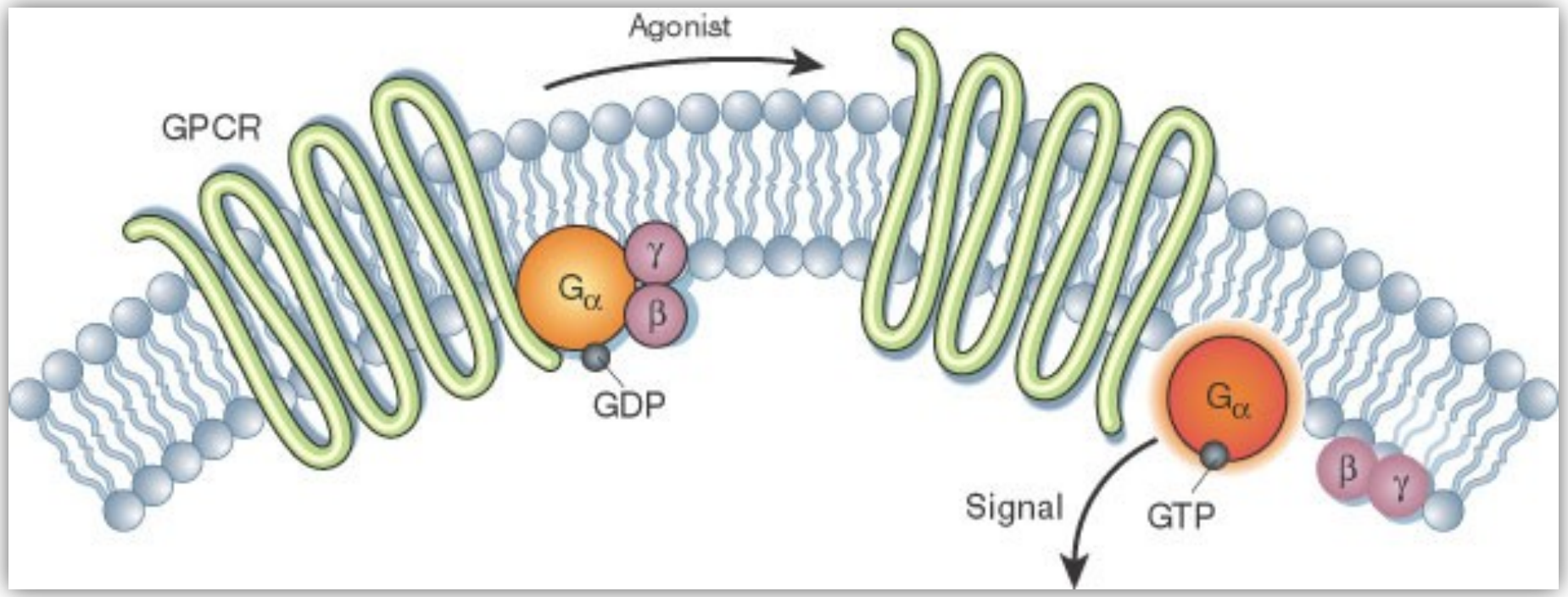
- **Receptors**: CB1 & CB2 – G-protein coupled receptor type (GPCR)
- **Ligands**: Anandamide & 2-AG – endocannabinoids
- Endocannabinoid **biosynthesis enzymes**:
  - DAGL à 2-AG
  - NAPE-PLD à Anandamide
- Endocannabinoid **break down enzymes**:
  - MAGL à 2-AG
  - FAAH à Anandamide

...and is located throughout our bodies



- More CB1 than CB2
- **CB1** found in high concentrations in **brain regions**; fat tissue; liver; pancreas, and skeletal muscle cells
- CB1 is the most abundant **GPCR** in the brain
- **CB2** found in most cells of the **immune system**

GPC (or 7-transmembrane) receptors, signal via 2nd messenger pathways



Cannabinoid receptors are involved in a wide variety of effects

- CB1
  - Regulates learning and memory
  - Neuronal development and synaptic plasticity
  - Regulates reward and addiction (*alcohol, nicotine*)
  - Reduces pain
  - Regulates metabolism and food intake (*incl. weight gain*)
  - Regulates bone mass
  - Cardiovascular effects
- CB2
  - Allergic and autoimmune inflammatory disease
  - Osteoporosis
  - Neurodegenerative disease
  - Ischemic injury from stroke or heart attack
  - Chronic pain

Other GPCR targets of cannabinoids

- GPCR18 – Immune system; anti-inflammatory, lowers blood pressure, modulates immune function
- GPCR55 – Pancreas; insulin release (diabetes, obesity, metabolism), lowers blood pressure, anti-inflammatory
- GPCR19 – Pancreas and GI tract; regulates energy intake

Additional molecular targets of cannabinoids

- TRP channels
- Glycine receptors (GlyR)
- Serotonin receptors (5HT)
- Peroxisome Proliferator-Activated receptors
- Dopamine receptors
- Opioid receptors
- GABA receptors
- Acetylcholine receptors

***Take away:** cannabinoid – receptor interactions are extremely complex and go beyond CB1/CB2. We are just scratching the surface
More studies need to be done!

Challenges of cannabinoid administration

- Inconsistent quality, varying potency, different formulations, *etc.*
- Cannabinoids are not single target drugs.
- Significant interindividual variability.
- Incomplete understanding of the Endocannabinoid System (ECS).

Bioavailability

- A function of drug absorption by the body.
- A measurement of the rate and extent to which a drug reaches the site of action.
- When a drug is administered intravenously its bioavailability is considered 100%.
- This value typically drops when other forms (*e.g.* oral) of administration are used.

Bioavailability as a function of route of administration

- Smoking
  - 3-10 minutes for peak plasma concentrations
  - 10-35% bioavailability (23-27% for heavy users and 10-14% for occasional users) – also a function of smoking topography.
- Oral Administration
  - Slow and erratic, 60-120 minutes for peak (as long as 4-6 hours in some cases).
  - 1st pass hepatic metabolism, 4-14% bioavailability.
- Ophthalmic Administration
  - 6-40% bioavailability in rabbits, plasma peak up to several hours.

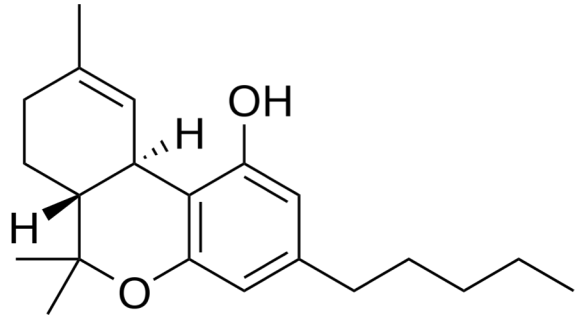
Bioavailability as a function ofroute of administration

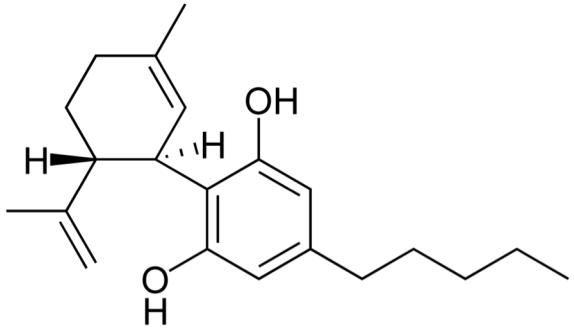
- Rectal Administration
  - Depends on formulation
  - 13.5% bioavailability
- Transdermal Administration
  - No absolute bioavailability known
- Sublingual/Buccal Administration
  - Similar to oral bioavailability

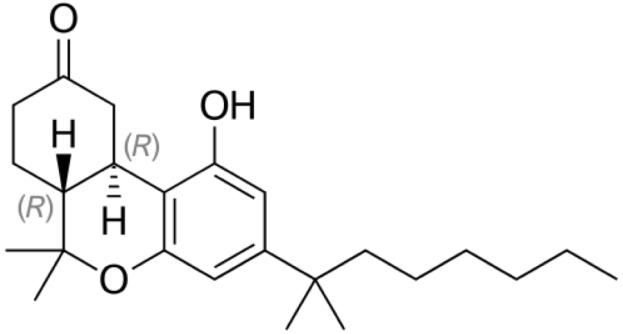
There are different types of cannabinoids

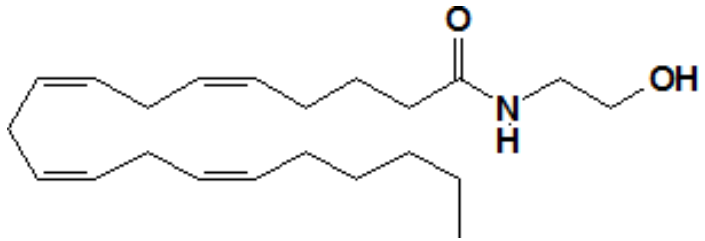
- Phytocannabinoids – THC, CBD, *etc*.
- Endocannabinoids – 2-AG, AEA, *etc*.
- Synthetic cannabinoids – Nabilone, Rimonabant, *etc*.

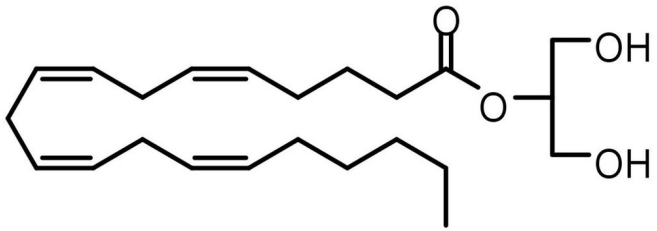
Chemical structures of cannabinoids

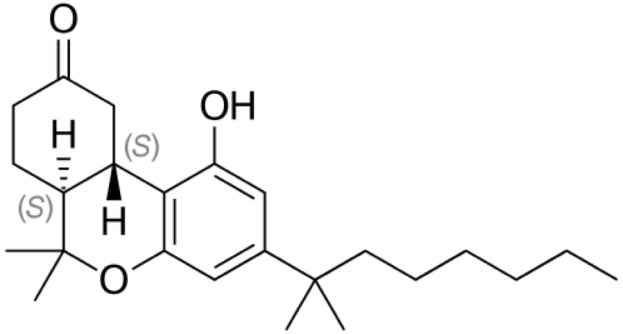


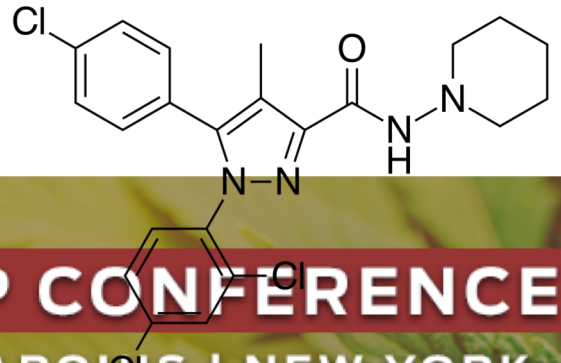












Theory *vs.* practice…

- How does what we know about the biochemistry of cannabinoids and their receptor interactions translate into practice…?
- Lots of anecdotal evidence for numerous conditions.
- What about clinical controlled studies?

International Association for Cannabis as Medicine (IACM)

- National Academies of Sciences, Engineering and Medicine published a report in January 2017
- Searched through over 24,000 literature articles
  - Conclusive or substantial evidence that cannabinoids are effective for pain, chemotherapy induced nausea/vomiting (CINV), epilepsy and spasticity associated with MS
  - Moderate evidence that cannabinoids are effective for sleep disturbances associated with different diseases
  - Limited evidence to support or refute that cannabinoids are effective for cancer, IBS, neurodegenerative diseases such as Parkinson's, ALS, and Huntington's disease
  - Significant barriers preventing research on cannabinoids in the US

Future and potential indications

- Potential indications from pre-clinical and animal studies:
  - Crohn's disease – 18 patient study using cannabis oil and placebo; cannabis had a positive effect on the quality of life and CDAI for patients
  - Cancer – 2,730 cancer patients, 95.8% reported improvement in their conditions for palliative treatment
  - ADHD – single patient case study, cannabis was found to provide safe and effective treatment particularly when other CNS drugs were ineffective

Future and potential indications

- Continued…
  - Older subjects – 937 patients 65 years or older, using cannabis for a number of different indications, 87.7% reported an improvement in their quality of life
  - Cancer – mouse model showed that cannabis can reduce tumor growth, including melanomas, carcinomas, and gliomas
  - Age associated cognitive decline and cognitive decline from hypoxia, deep anesthesia, MDMA-toxicity, epileptic seizures or neuroinflammation – mouse model study, microdose of THC (0.002 mg/kg) effectively treated cognitive decline

Future and potential indications

- Continued…
  - Acne, Allergies, Anorexia and cachexia, Anxiety disorder, Asthma, ADHD, Autism, Barrett's oesophagus, Bladder spasms, Blepharospasm, Borderline personality disorder, Cervical and lumbar spine syndrome, Cervicobrachialgy, CFS, Chronic pain syndrome after polytrauma, Cluster headaches, Head injuries, Crohn's disease, Dejerine-Roussy syndrome after stroke, Depression, Epilepsy, Failed back surgery syndrome, Fibromyalgia, Headache, Hereditary motor and sensory neuropathy with pain and spasms, HIV, Hyperhidosis, PTSD, RA, Restless leg syndrome, Lupus, Lyme disease, OCD, Psoriasis, Tourette's syndrome, etc etc etc…
  - MORE STUDIES NEEDED!!

- Some of these drugs have been around since the 1980's
- Every state has their own list of conditions that qualify for cannabinoid therapy. This is often not science-based
- Sativex and Cannador are not approved in the US

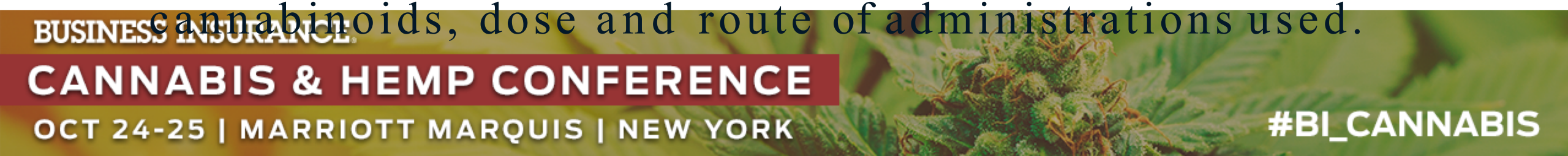
Substance	Details	Route of Administration	Indication	Recommended dose
Sativex® (Nabiximols)	Whole plant extract ~1:1 THC:CBD	Oromucosal spray	Pain and spasticity associated with Multiple Sclerosis.	1-spray or 100 mL twice daily (contains 2.7 mg THC and 2.5 mg CBD)
Cesamet® (Nabilone)	Synthetic cannabinoid	Oral capsules (1 mg nabilone per capsule)	Chemotherapy Induced Nausea and Vomiting (CINV).	1 or 2 mg twice daily during Chemotherapy treatments. Maximum dose – 6 mg per day.
Marinol® (Dronabinol)	Synthetic THC	Oral liquid capsules (2.5, 5 or 10 mg per capsule) Oral solution, 5 mg/mL	Anorexia associated with weight loss in AIDS patients. CINV.	2.5 mg orally twice daily, one hour before lunch and dinner. Maximum dose – 10 mg twice daily.
Epidiolex®	CBD	Oral solution, 100 mg/mL	For the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet Syndrome (DS) in patients 2 years and older.	2.5 mg/kg twice daily . Maximum dose – 10 mg/kg twice daily.
Cannador®	Whole plant extract in a 2:1 ratio of THC:CBD	Oral capsule	Pain and spasticity associated with Multiple Sclerosis. CINV.	10 mg daily.

Caution is needed with the interpretation of study outcomes

- "The most important principle in administering cannabinoids is **gradual dose titration** to ensure optimum benefit with minimum side effects."

- "It is impossible to predict the dose at which benefit or side effects will start to emerge for an **individual patient** …"

- Studies are often **difficult to compare** due to different cannabinoids, dose and route of administrations used.



Conclusions (1/2)

Knowns:

- Cannabinoids exhibit an **interesting therapeutic** option as antiemetics, appetite stimulants, analgesics, treatment for MS, spinal cord injuries, Tourette's syndrome, and epilepsy.

- Synthetic cannabinoids (nabilone and dronabinol) are not popular in clinical studies due to the narrow gap between therapeutic threshold and tolerability threshold.

- Clinicians are hesitant to use smokable cannabis inclinical trials.

Conclusions (2/2)

Unknowns:

- **Many diseases** haven't been studied well with regards to cannabinoid effects.

- Most of the **effect variability** between people has an unknown origin (*i.e.* why there is so much variability between individuals is unknown).

- For each pathology, it remains to be determined what type of cannabinoid, what route of administration and what dose are **most suitable to maximize beneficial effects**.

MORE RESEARCH IS NEEDED

Thank you!
Questions…?

References can be provided upon request

jeremy@marysmedicinals.com