

## Slide – Endocannabinoid System

“The endocannabinoid system has been implicated in a very broad number of physiological as well as pathophysiological processes including neural development, immune function, inflammation, appetite, metabolism and energy homeostasis, cardiovascular function, digestion, bone development and bone density, synaptic plasticity and learning, pain, reproduction, psychiatric disease, psychomotor behaviour, memory, wake/sleep cycles, and the regulation of stress and emotional state”

### **Receptors:**

CB1 & CB2 are G-coupled protein receptors that signal the G1/G0 dependent signaling cascades (cAMP & such)

The CB1 receptor is one of the most abundant G-protein coupled receptors in the central and peripheral nervous systems (17).

\*\*\*Flip to next slide, then come back\*\*\*

The CB1 receptor is also expressed in many other organs and tissues including adipocytes, leukocytes, spleen, heart, lung, the gastrointestinal tract (liver, pancreas, stomach, and the small and large intestine), kidney, bladder, reproductive organs, skeletal muscle, bone, joints, and skin

CB2 receptors are most highly concentrated in the tissues and cells of the immune system such as the leukocytes and the spleen, but can also be found in bone and to a lesser degree in liver and in nerve cells.

### **Endocannabinoids:**

The two most well understood of these molecules are called [anandamide](#) and [2-arachidonoylglycerol \(2-AG\)](#). They are synthesized on-demand from cell membrane arachidonic acid derivatives, have a **local effect and short half-life** before being degraded by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL).

(Anandamide is derived from Sanscrit word for “Bliss” – Runner’s High chemical)

## Slide – Exogenous Cannabinoids

### **Phytocannabinoids:**

- Concentrated in trichomes on the leaves & buds
  - Delta 9 tetrahydrocannabinol – primary psychoactive molecule
  - Cannabidiol (CBD) – primary non-psychoactive molecule
  - Cannabinol (CBN) – main degradation product
  - CBG, CBC, ~60-70 others
- Indica
  - High THC & CBD
  - sedative/relaxing (stoned), centered in the body
  - smaller plants, denser, broad leaves
- Sativa
  - High THC

- Energizing/uplifting (high), centered in the head
- Taller plants, smaller, long thin leaves
- Ruderalis – not very psychoactive

### Slide – Indications:

- Delta 9 tetrahydrocannabinol – primary psychoactive molecule
  - Analgesic at CB1 & CB2, anti-emetic, anti-inflammatory, antioxidant, anti- duodenal ulcer, anti-alzheimer’s, anti-itching, bronchodilatory, muscle relaxant
- Cannabidiol (CBD) – primary non-psychoactive molecule
  - Anandamide reuptake inhibitor
  - Analgesic, anti-convulsant, antidepressant (in rodents), anti-emetic, anti-fungal, anti-inflammatory, antioxidant, anxiolytic (serotonin agonist), anti-sebum (blackheads & pimples), **anti-MRSA**, pro-apoptosis in breast cancer lines, treatment of psychosis & addiction
  - Antagonizes THC effect

### Slide – Dosing:

\*\*\*After “Highly Individualized” flip to Table 2\*\*\*

#### **Dosage Forms:**

- Inhaled / IV
  - Rapid onset within seconds to minutes
  - Max effect – 30 minutes, 2-3 hour duration
  - ~50% THC delivered through the smoke
  - 10-25% metabolized in the lungs
- Oral
  - Onset 30 minutes – 2 hours
  - Duration – 5-8 hours
  - Highly variable, titration difficult
  - 5-20% bioavailable (significant 1<sup>st</sup>-pass effect)
  - Empty stomach, full glass of milk (not skim, lipophilic)

### Slide – Table 2:

#### Impairment

- Impairment thresholds are between 2-5 ng/ml
- Significant impairment in 75-90% of tests 5-10 ng/ml
- Significant impairment in 100% of tests >30ng/ml

Plasma concentrations of 50-100 ng/ml are needed to get the “high”, and one cigarette of 3.55% THC reaches on average 162 ng/ml

National Institute on Drug Abuse (NIDA)

- 1.64% - Plasma 77ng/ml – 13mg THC
- 1.80% - Plasma 75ng/ml – 14mg THC
- 3.60% - Plasma 100ng/ml – 28.8mg THC

\*\*\*Take home message – Very small quantities of the current average of 10% THC would be needed\*\*\*

\*\*\*Flip back to Dosing Slide\*\*\*

## Slide – Drug Interactions

\*\*\*Do not read, here for reference if questions\*\*\*

### *Xenobiotic-mediated inhibition or potentiation of cannabinoid metabolism*

$\Delta^9$ -THC is oxidized by the xenobiotic-metabolizing cytochrome P450 (CYP) mixed-function oxidases 2C9, 2C19, and 3A4 (62). Therefore substances that inhibit these CYP isoenzymes such as certain anti-depressants (e.g. fluoxetine, fluvoxamine, and nefazodone), proton pump inhibitors (e.g. cimetidine and omeprazole), macrolides (e.g. clarithromycin and erythromycin), anti-mycotics (e.g. itraconazole, fluconazole, ketoconazole, miconazole), calcium antagonists (e.g. diltiazem, verapamil), HIV protease inhibitors (e.g. ritonavir), amiodarone, and isoniazid can potentially increase the bioavailability of  $\Delta^9$ -THC as well as the chance of experiencing THC-related side effects (289,875,876). On the other hand, drugs that accelerate  $\Delta^9$ -THC metabolism via 2C9 and 3A4 isozymes such as rifampicin, carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, troglitazone, and Saint John's Wort may conversely decrease the bioavailability of THC and hence its effectiveness if used in a therapeutic context (289,876).

## Slide – Adverse Events

### Schizophrenia

- Endocannabinoids help regulate synaptic pruning which is very active during adolescent brain changes
- Imaging studies – adverse effects on hippocampus and cerebellum development
- 2-fold increase of schizophrenia development with early, heavy use
- Continued use in schizophrenia leads to more severe psychosis

## Slide – Single Convention

### *Article 28*

#### CONTROL OF CANNABIS

1. If a Party permits the cultivation of the cannabis plant for the production of cannabis or cannabis resin, it shall apply thereto the system of controls as provided in article 23 respecting the control of the opium poppy.
2. This Convention shall not apply to the cultivation of the cannabis plant exclusively for industrial purposes (fibre and seed) or horticultural purposes.
3. The Parties shall adopt such measures as may be necessary to prevent the misuse of, and illicit traffic in, the leaves of the cannabis plant.

### *Article 23*

#### NATIONAL OPIUM AGENCIES

1. A Party that permits the cultivation of the opium poppy for the production of opium shall establish, if it has not already done so, and maintain, one or more government agencies (hereafter in this article referred to as the Agency) to carry out the functions required under this article.

2. Each such Party shall apply the following provisions to the cultivation of the opium poppy for the production of opium and to opium:

- a) The Agency shall designate the areas in which, and the plots of land on which, cultivation of the opium poppy for the purpose of producing opium shall be permitted.
- b) Only cultivators licensed by the Agency shall be authorized to engage in such cultivation.
- c) Each licence shall specify the extent of the land on which the cultivation is permitted.
- d) All cultivators of the opium poppy shall be required to deliver their total crops of opium to the Agency. The Agency shall purchase and take physical possession of such crops as soon as possible, but not later than four months after the end of the harvest.
- e) The Agency shall, in respect of opium, have the exclusive right of importing, exporting, wholesale trading and maintaining stocks other than those held by manufacturers of opium alkaloids, medicinal opium or opium preparations. Parties need not extend this exclusive right to medicinal opium and opium preparations.

**3. The governmental functions referred to in paragraph 2 shall be discharged by a single government agency if the constitution of the Party concerned permits it.**

### **Slide – Pro-Cannabis Countries**

**Uruguay:**

- Purchase – 40 grams per month from licensed pharmacies
- Grow – 6 plants per year or up to 480 grams per year
- Form smoking clubs of 15-45 members – up to 99 plants per year

### **Slide - Netherlands**

Clean Rooms, Good Manufacturing Practice compliance, Certificate of Analysis required for each batch, etc.

### **Slide – Background**

**August 29, 2013 Memorandum:**

- DOJ Priorities include:
- Preventing distribution to minors
- Preventing revenue from the sale of marijuana from going to criminal enterprises, gangs, and cartels
- Preventing the diversion of marijuana from states where it is legal under state law in some form to other states
- Preventing state-authorized marijuana activity from being used as a cover or pretext for the trafficking of other illegal drugs or other illegal activity
- Preventing violence and the use of firearms in the cultivation and distribution of marijuana
- Preventing drugged driving and the exacerbation of other adverse public health consequences associated with marijuana use
- Preventing the growing of marijuana on public lands and the attendant public safety and environmental dangers posed by marijuana production on public lands; and
- Preventing marijuana possession or use on federal property

## **Slide – Recent National Developments**

### **Cromnibus passage means:**

- by Act of Congress, it forbids the spending of money by DEA, the U.S. Attorney and other elements of the U.S. Department of Justice from interfering with Maryland in implementing our medical marijuana law.
- This moves the situation out of the discretion of the Attorney General and the question of whether the various memoranda issued by the Deputy Attorney General in recent years regarding marijuana will survive the retirement of Attorney General Eric Holder, or the Obama Administration.
- It means that all of the doctors who want to write written certifications under our program, and provide advice to their patients, do not have to worry about losing their DEA registrations to prescribe controlled substances.
- It means that all of the investors and applicants for licenses to grow, process or dispense medical marijuana under our regulations do not have to worry about prosecution for growing and distributing medical marijuana or for engaging in financial transactions from the proceeds of the growing and distribution of medical marijuana.
- It means that the commissioners and staff of the commission who are engaged in facilitating the cultivation of medical marijuana have no worry about prosecution.
- It means academic medical centers might consider participation in the medical marijuana research program if they thought the research questions were important enough, and they had staff and funding, etc.

This section only addresses medical marijuana programs and does not address legalization question.

## **Slide – MMJ Laws around the Country**

- 1996 – California
- 1998 – Congress blocks District of Columbia from counting votes on a referendum
- 1998 – Alaska, Oregon, Washington
- 1999 – Maine
- 2000 – Hawaii, Colorado, Nevada
- 2004 – Vermont, Montana
- 2006 – Rhode Island
- 2007 – New Mexico
- 2008 – Michigan
- 2010 – New Jersey, District of Columbia, Arizona, South Dakota voters rejected 63% to 37%
- 2011 – Delaware
- 2012 – Connecticut, Massachusetts
- 2013 – New Hampshire, Illinois
- 2014 – Maryland, Minnesota, New York

## **Slide – The Regulations**

The Commission referenced Nevada, Arizona, Illinois, Connecticut, D.C. as well as Colorado, but wrote mostly everything from scratch due to unique features of the Maryland law.