What is known about the clinical pharmacology of medical cannabis?

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Disclosure Statement

• Dr. Franson has no financial investments and receives no funding from any of the private companies talked about in this presentation.

• Dr. Franson will be discussing unapproved drugs and unapproved uses for drugs.

At the end of the session, participants will be able to:

1) explain what cannabis does to the human body with a focus on THC & CBD (pharmacology)
2) compare the various routes of cannabis administration and how the human body manages the drug (pharmacokinetics)
3) evaluate new Colorado Amendment 64 legislation considering what is known about clinical pharmacology
Pharmacology
Cannabis (sativa, indica, ruderalis)

Plant-derived cannabinoids

- $\Delta^9$-tetrahydrocannabinol (9) - THC
- $\Delta^9$-tetrahydrocannabivarin - THCV
- Cannabidiol (7) - CBD
- Cannabigerol (6)
- Cannabichromene (5)
- Cannabicyclol (3)
- Cannabielsoin (5)
- Cannabinol (9)
- Cannabinol
- Miscellaneous (11)
Cannabinoid/CB receptor interactions
Cannabinoid receptor active ligands

- full agonist (HU-210)
- partial agonist (THC & anandamide)
- antagonist (surinabant)
- partial inverse agonist (CBD)
- agonist + antagonist (THC + surinabant)
- agonist + inverse agonist (THC + CBD)
Normal neurotransmission
Regulatory effects of cannabinoids

Pertwee RG, Br J Pharm, 2008
Normal neurotransmission in a network

pre-synaptic neuron

stimulus

ATP

Ca^2+

cAMP

AC

post-synaptic neuron

less cellular effect
Regulatory effects of cannabinoids

Pertwee RG, Br J Pharm, 2008
Distribution of CB1 & CB2 receptors

CB1
- neocortex (thinking)
- basal ganglia (motor activity)
- hypothalamus (appetite)
- nucleus accumbens (reward)
- hippocampus (short term memory)
- cerebellum (motor coordination)
- periaqueductal gray dorsal horn (pain)

CB2
- immunologic cells (modulation cell migration)
- microglia (possible role in Alzheimer’s?)
Cannabis effect on reward pathway

DA: reward and motivation

Glu: learning and memory

GABA: inhibition of neuronal activity
Brain development in adolescence

Accumbens
- Immediate rewards
- Impulsive behavior

Cortex
- Long term gain
- Thoughtful behavior

Amendment 64 prohibits the sale and use of cannabis products by those younger than 21 years. Why?

The adolescent brain is still developing. There is concern that the reward pathways and feedback loops may be altered if cannabis is used by those with still developing brains.
Non-cannabinoid targets linked to cannabis

- Other G-protein receptors: GPR55, GPR55940, etc
- G-protein-coupled receptors: noncompetitive inhibitor at μ- and δ-opioid receptors, NE, DA, 5-HT
- Ligand-gated ion channels: antagonism at 5-HT3, nicotinic, and enhance activation of glycine receptors
- Transient receptor potential channels (TRPVs): bind and activate TRPV1 similar to capsaicin, also CB1 receptors are located near TRPV1
- Ion channels: inhibition of Ca, K, Na channels by non-competitive antagonism
- Peroxisome Proliferator-Activated Receptors: PPARα and PPARγ are activated

Pertwee RG, Pharma Rev 2010
What is in medical cannabis?

Strain: White Widow
Primary Cannabinoid: THC    Ratio: %

Calculated Active Cannabinoids
- CBD: 0.49%
- CBC: 0.02%
- CBN: %
- THCV: 0%
- THC: 15.33%

Total Active Cannabinoids: 15.95%

Find out what's in your meds so you can understand what you're buying before you buy it.

Strain Reviews

Find Your Perfect Strain

www.fullspectrumlabs.com  Accessed 07/18/2011
To review:

What does THC do to the human body?
- it is a partial agonist for the CB1 receptor
- CB1 receptors regulate the release of other neurotransmitters
- CB1 receptors are primarily located in the brain; effecting thinking, memory, appetite, reward and movements
- It is the most psychoactive substance in cannabis

What does CBD do to the human body?
Pharmacokinetics
Pharmacokinetic profile of THC

Smoking:

• Bioavailability: 10-25%
  50% of the THC content is delivered into smoke
  50% of smoke is exhaled again
  60% of inhaled smoke may be metabolized in the lung

• Peak concentrations are high and reached within minutes

• t½ distribution 0.5 hr,
  t½ for elimination 30 hr

Agurell S, 1986; Strougo A, 2005
Vaporization of medical cannabis

- Cannabinoids vaporize at a temp lower than combustion
- Increasingly popular
- Lower % of noxious chemicals

Pharmacokinetic profile of THC

Oral:

• Bioavailability: 5-20%
  Often considered 1/3 that of smoked due to gastric degradation and extensive first-pass effects
  High intra-patient variability!
• Multiple peak concentrations are low and reached in 1-3 hr
• $t_{1/2}$ absorption 0.8 hr, $t_{1/2}$ distribution 3.8 hr
  $t_{1/2}$ for elimination 25 hr

Agurell S, 1984; Ohlsson A, 1980
THC is the most psychoactive component of cannabis

Typical “effective” dosing of THC
- Low dose < 7 mg
- Medium dose = 7 – 18 mg
- High dose > 18 mg

There is a known tolerance to THC via down regulation of CB1 receptors
High probability of tolerance with chronic use, and low with intermittent

Zuurman L, Brit J Clin Pharm 2009
CO HB 13-1317 labeling of product

• A net weight statement;
• THC potency and the potency of such other cannabinoids or other chemicals, including but not limited to CBD,
• A serving size for edible retail marijuana products that does not contain more than ten milligrams of active THC, ..., and limitations on the total amount of active THC in a package that is no more than one hundred milligrams of active THC;
How much should a person use to get 25 mg of THC?

- 20% THC
- Net weight 1/8 oz or 3.5 gm
- Single serving 50 mg
The pharmacodynamics of THC

- Evaluated 165 studies to determine consistently found PD effects
  - Elevation in heart rate (average >19 bpm)
  - Increase in subjective feeling high
  - Decrease in subjective alertness
  - Increase in motor instability (body sway)

Zuurman L, Brit J Clin Pharm 2009
PK/PD modeling of THC

- Subjects given increasing doses (2, 4, 6, 8 mg) of THC via Volcano vaporizer at 1.5 hr intervals

Adapted from Zuurman L, Brit J Clin Pharm 2009
PK/PD modeling of THC

Heart rate (bpm)

VAS feeling high (U)

VAS alertness (mm)

Adapted from Zuurman L, Brit J Clin Pharm 2009
A man in a MVA is found to have a blood THC level of 10 ng/ml. House Bill 1325 set THC limit at 5 ng/ml

1. The man did not reach the level of impairment
2. The man was above the known level of impairment
3. The level of presumptive impairment is not known
4. It is not known if the man was impaired with this concentration
Population response to medical cannabis

- **Hormones:**
  - Males: decreased LH, FSH, prolactin, and GH levels
  - Females: more sensitive to THC effects (pain, behavior, reward) with higher estrogen levels

- **Tobacco:** greater increases in HR and carbon monoxide, despite lower THC concentrations

- **MDMA:** synergistic impairment in working memory

- **CV patients:** ↑HR and ↓HRV with cannabis use
Acute toxicities

- Hallucinations
- Tachycardia
- Labored breathing
- Obtundation

Wang GS JAMA Pediatrics, 2013

http://opiophilia.blogspot.com/2013_04_01_archive.html
To review:

What does the human body do to THC?

– Smoking THC mimics IV, but with 10-25% bioavailability, quick effect → easy to titrate
– Ingesting THC, 1/3 bioavailability, high variability and delayed effect → increased toxicities
– Medium dose ≈ 10mg, giving rise to ↑HR, ↑high, ↓alertness, ↓stability, but tolerance quickly develops
– Acute THC ingestions are relatively safe
Wrap-up from today’s session

1) Explained the pharmacology of THC & CBD
2) Compare the pharmacokinetics with various forms of cannabis
3) Examined new Colorado legislation considering what is known about clinical pharmacology
4) Questions?