CANNABIS

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Disclosure

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LECTURE OUTLINE:

CANNABIS
1) GENERAL BACKGROUND
2) EPIDEMIOLOGY
3) BIOLOGY/BASIC CHEMISTRY
4) PHARMACOLOGY
5) CLINICAL EFFECTS
6) ADDICTION
6) ADVERSE EFFECT OF CANNABIS
7) TREATMENT
8) METABOLISM / DRUG TESTING
9) MEDICAL CANNABIS
10) MEDICAL MARIJUANA REGULATIONS
GENERAL BACKGROUND

Cannabis (CB):
Name given to preparations of the Cannabis Sativa plant
Used > 5000 years: medical and recreational purposes
Used as a medicine in China (2700 BC) and India (1000 BC)

CB entered Western medicine in early and middle 19th century
Used widely for its medicinal properties
Commonly used recreationally as Marijuana
Marijuana: dried leaves and flowers of the C. Sativa plant
Smoked as joints, heated with a vaporizer and inhaled
EPIDEMIOLOGY

CB use:

is one of the most widely used drugs in the world[^1]

about 4% of the world’s population between 15 - 64 years use CB in past year

22-28% of ages 14-24 and 7% over 25 admit to use in past year

Of those who use CB, 9% develop CB use disorder

Comparison: 16% for Alcohol, 33% for Nicotine.
**BIOLOGY/BASIC CHEMISTRY**

*Cannabis Sativa* plant: 483 unique compounds, 66 cannabinoids (21-Carbon containing terpene-like compounds, found uniquely in these plants)

THC (9-Delta Tetrahydrocannabinol) is the primary psychoactive compound produced by CB best studied constituent of the CB plant

THC content of marijuana has increased from 1-5% to 10-15% over last 40 years

CBD (cannabidiol) – is the most commonly occurring non-psychoactive cannabinoid
Cannabinoid class divisions:

1. Phyto-cannabinoids (have plant origin)
   Δ-9-tetrahydrocannabinol (THC), Cannabidiol (CBD)

2. Endocannabinoids (present endogenously in human or animal tissues)
   Anandamide (arachidonoyl ethanolamide)
   2-arachidonoyl glycerol (2-AG) / 2- arachidonyl glyceryl ether (noladin ether)
   virodhamine
   N-arachidonoyl-dopamine (NADA)

3. Synthetic cannabinoids
   Dronabinol : synthetic THC
   Nabilone : a synthetic derivative of THC
Native receptors for Cannabinoids known as Cannabinoid receptors, or CBRs

Two CBRs: CB1-R and CB2-R have been cloned from various animal species, including humans.

CBRs belong to a superfamily of G protein-linked receptors.

CBRs found in variety of tissues: brain, peripheral tissues including sensory nerve fibers, autonomic nervous system, immune cells.
CB1-R receptor is predominantly expressed on neurons.

CB1-R is present in high levels in: hippocampus, lateral part of the striatum, globus pallidus, entopeduncular nucleus, substantia nigra, pars reticulata, and cerebellar molecular layer.

CB1-R is matched to endogenous ligands.

Endocannabinoids function primarily as Neurotransmitters/neuromodulators.
PHARMACOLOGY

Most CB1-R receptors are found pre-synaptically and can modulate NTs release through pre-synaptic inhibition

- can lead to decreased release of other NTs: Glutamate, GABA, norepinephrine, dopamine, serotonin, acetylcholine

CB1-R-activation suppresses the Nociceptive sensitization by influencing the release of Neurotransmitters: acetylcholine, norepinephrine, GABA, glycine, dopamine, serotonin

- important in analgesic effect of CB
PHARMACOLOGY

CB2-Rs are found mainly in the periphery i.e. immune system: monocytes, macrophages, B Cells, and T-Cells and in tissues of the spleen, tonsils, and thymus gland.

Increased CB2-R expression found in spinal cord, dorsal root ganglion

The principal endogenous ligand for the CB2-R is 2-AG

CB2-R involved in: modulatory functions:
- immune suppression
- induction of apoptosis
- induction of cell migration
CLINICAL EFFECTS

Smoked CB: rapid absorption and onset of psychoactive effects is preferred mode of recreational use

Ingestion of hashish:
- delayed onset and longer duration of action

CB HIGH:
- Marked by a euphoric, pleasurable feeling; decreased anxiety and alertness; depression

First-time CB users, as well as anxious, and psychologically vulnerable individuals, may experience:
- anxiety
- dysphoria
- panic symptoms
CLINICAL EFFECTS

CANNABIS HIGH

CB user is sought for:
Perceptual changes that include:
    - the sensation that colors are brighter
    - that music is more vivid
    - time perception and spatial perception distortions

“When I was a kid I inhaled frequently. That was the point.”
– Barack Obama
CLINICAL EFFECTS

CANNABIS INTOXICATION

Psychological signs:
- Hallucinations.
- Increased self consciousness
- Depersonalization
- Paranoia
- Psychosis

Physiologic Signs:
- Tachycardia
- Hypertension
- Conjunctival injection
- Dry mouth
- Increased appetite
Acute adverse reaction during CB Intoxication can mimic other existing mental health conditions, such as:

- Panic disorder
  - Generalized anxiety disorder
  - Major depressive disorder
  - Bipolar disorders
- Schizophrenia, especially paranoid type
SUBJECTIVE EFFECTS:
- Enhancement of senses
- Errors in space and time judgment
- Emotional instability
- Impulsivity
- Illusions
- Hallucinations
- Symptoms similar to Dysthymic disorder
CLINICAL EFFECTS

CANNABIS CHRONIC USE

Users using more than 1g/day for > several months or more may experience:

OBJECTIVE EFFECTS:
- Cognitive impairments
- Decreased psychomotor performance
- Attention difficulties
- Decreased concentration
- Short term memory impairment
- Tachycardia
- Immunosuppression effects
CANNABIS USE DISORDER

DSM V- Diagnostic Criteria for Cannabis Use Disorder (CB-UD)

A problematic pattern of CB use leading to clinically significant impairment or distress, as manifested by 2 or more of the following within a 12-month period:

CB is taken in larger amounts or over a longer period than was intended
Persistent desire or unsuccessful efforts to cut down or control CB use
Great deal of time is spent in activities necessary to obtain CB, recover from its effects
Craving/Strong desire or urge to use CB
Recurrent CB use resulting in a failure to fulfill major role obligations at work, school, or home
Continued CB use despite having recurrent harms
Tolerance
Withdrawal
CANNABIS USE DISORDER

DSM V- Diagnostic Criteria for Cannabis Use Disorder

The severity of cannabis use disorder at the time of diagnosis can be specified as a subtype based on the number of symptoms present:

Mild: Two to three symptoms
Moderate: Four to five symptoms
Severe: Six or more symptoms
CANNABIS USE DISORDER

Cannabis Withdrawal Syndrome

Typically begins on the first or second day of abstinence, peaks between day two to six and resolves within seven to fourteen days

Symptom:
- cravings for CB
- decreased appetite
- insomnia
- nightmares
- agitation
- restlessness
- irritability
- sleep disturbance
CANNABIS USE DISORDER

Cannabis Withdrawal Syndrome

THC characteristically redistributes quickly into body fat

Extends its elimination half life and may lessen the severity of withdrawal symptoms: but extends their duration

CB withdrawal can be uncomfortable or distressing but is not life threatening
CANNABIS USE DISORDER

CB REWARD

Mostly derived from increase in Dopamine (DA) in meso-corticolimbic pathways involved with reinforcement/reward

Supplemented by interaction with opioid systems

THC: stimulates DA-ergic neurons in the Ventral Tegmental Area (VTA)

Cannabinoids can induce the synthesis and release of endogenous opioid peptides
ADVERSE EFFECTS

LONG TERM MEDICAL COMPLICATIONS

PULMONARY
CB smoke irritates the airways associated with cough, sputum production, wheezing, bronchodilatation, bronchitis, dyspnea, exacerbation of asthma, and exacerbation of cystic fibrosis.

CARDIOVASCULAR
CB smoke risk for older people with CAD or CVD due to increased catecholamine, increased carboxyhemoglobin levels, increased cardiac work. CB in high doses inhibit sympathetic activity, increase parasympathetic activity. Leads to bradycardia and hypotension.
ADVERSE EFFECTS

CANCER

Established mutagen (carcinogen) benzo-pyrene, is present in CB Smoke Condensate (CBSC) at 70% higher than tobacco smoke condensate (TSC)

CBSC leads to

- 5X increase in blood carboxyhemoglobin level
- 3X increase in inhaled tar compared to TSC
- retention in respiratory tract on 33% more inhaled tar
- 66% larger “puff volume” than TSC
- 33% greater depth of inhalation than TSC
- 4X longer breath holding time than TSC
CB USE IN PREGNANCY

Effects largely unknown, due to lack of rigorous study

Linked to
Neuro-developmental defects
Attention Deficit Hyperactivity Disorder

CB hyperemesis syndrome

Chronic heavy CB use can cause recurrent episodes of severe nausea, intractable vomiting, and abdominal pain
Resolves when cannabis use is stopped
ADVERSE EFFECTS

**IMMUNE SYSTEM**
CB use appears to suppress aspects of immunological function
Uncertain if clinically relevant change in infections rate

**ENDOCRINE**
CB suppresses
secretion of testosterone in men
decreases libido, resulting in impotence gynecomastia
decreased sperm count and motility
may cause increased infertility
increases prolactin levels in women-> galactorrhea
ADVERSE EFFECTS

CB AND HIGHWAY ACCIDENTS
Ramaekers et al

CB is associated with motor vehicle collisions and motor vehicle injuries

Possible factors:

THC is a vasodilator, eye effects: loss of convergence/ability to cross; nystagmus; eye tracking abnormalities

Centrally, impairment in perception of speed and distance-time distortion effects

Drivers using cannabis are two to seven times more likely to be responsible for accidents compared to drivers not using any drugs or alcohol
ADVERSE EFFECTS

CB AND PSYCHOSIS/ADOLESCENCE

CB postulated to contribute to the development of schizophreniform disorders

Acute use of CB increases the risk of brief psychotic features

Adolescence is a sensitive period (active development of cortex and neuro-modulatory systems)

The later-maturing prefrontal cortex is more sensitive to adolescent CB exposure than the earlier-maturing, primary somatosensory cortex
Psychosocial interventions are preferred over medications for first line treatment of cannabis use disorder.

Psychosocial programs with demonstrated effectiveness:
- Cognitive behavioural therapy
- Motivational interviewing
- Voucher-based incentives (Contingency Management)

***None of these methods have been consistently shown to be superior to any other

Longer therapy has not been shown to have a better outcome

Review of RCTs show that psychotherapy is more likely to reduce CB use than lead to abstinence.
TREATMENT

No medications have been consistently shown to be effective for cannabis use disorder

A single randomized trial of N-acetylcysteine led to an increased likelihood of negative urine tests in patients with CB use disorder compared to patients receiving placebo.

Synthetic Cannabinoid agonists show promise in reducing symptoms of CB withdrawal and may also prevent relapse. Persistent withdrawal symptoms often contribute to relapse of cannabis use. *** Further study is needed.
TREATMENT

APPROACH TO SCREEN

Screen all patients once/year, youth and higher risk groups more often
Higher risk groups (adolescents, concurrent disorders)
Ask about CB use in past year, if yes, ask frequency and qty used
Patients using CB should be monitored for consequences
Validated Questionnaires (CRAFFT, MCQ)

MANAGEMENT

Provide brief advice/counseling to all patients with any use of CB, over
several sessions, usually as part of general visit
Establishing rapport is key to foster environment for counseling
Links between CB use and medical and personal harms elicited
Goal-oriented action specific conversations help to focus patients
Patients who stop CB use, and have severe withdrawal
symptoms may be admitted to Detox, or tapered using
prescription oral CB
If abstinence is goal, relapse is common: support is key
Refer to AMS MD if cannot stop/reduce use
DRUG TESTING

Useful for monitoring progress of treatment and early detection of relapse.

Intensive monitoring of substance use may increase recovery rates
Urine, blood, oral fluid, and hair can all be tested for cannabinoid metabolites
Urine testing most affordable, common and practical
A positive urine test only establishes past use and cannot be used to diagnose CB intoxication or a CB use disorder

Cannabinoid metabolites
highly lipophilic
persist in bodily fluids for extended periods of time
are excreted slowly
DRUG TESTING

Urine tests for CBDSs remain positive after discontinuation of CB for up to:

- 7 to 10 days in a casual CB user
- 2 to 4 weeks in a heavy user
- up to many months in a chronic heavy user
Binding of cannabinoids to CB-1 receptors is critical to their anti-nociceptive activity.

CBR-1 activation suppresses the nociceptive sensitization by influencing the release of neurotransmitters: acetylcholine, norepinephrine, gamma-amino butyric acid (GABA), glycine, dopamine, serotonin, cholecystokinin (CCK).
CB and PAIN

Nociceptive events in the body cause release of endocannabinoids

Endogenous Cannabinoids Anandamide, 2-arachidonoyl glycerol are potent analgesics!

Research: Cannabinoids have been found effective in increasing the threshold at which pain is perceived in tumor-afflicted mice

Adjunct use of cannabinoids in cancer-related pain may permit the use of lower doses of opioids

-> thus acting as an opioid-sparing agent in similar situations
MEDICAL CANNABIS

CB and PAIN

Smoked CB appears to have a role in
reducing neuropathic pain in HIV
relieving pain, spasticity, tremor, nocturia, improving general
well being in MS

CB and EMESIS

Endocannabinoid system modulates emesis
Cannabinoids are effective in treating Na and V associated with
chemotherapy, either by smoked CB or oral formulations
CBs act peripherally to regulate metabolism, energy balance and metabolism.

One of the consistent effects of oral or smoked CB is increasing appetite.
MEDICAL CANNABIS

CANADA: 3 cannabinoid products are available for medical use, more than in any other country worldwide.

1) Herbal CB extract (marketed as *Sativex* [GW Pharmaceuticals] which contains THC and CBD (Cannabidiol) in an oromucosal spray

2) *Nabilone* (a synthetic derivative of THC, marketed as *Cesamet* [Valeant Pharmaceuticals International])

3) Herbal form of CB (available legally through the Medical Marijuana Access Regulations)

*** *Dronabinol* (synthetic THC, marketed as *Marinol* [Solvay Pharmaceuticals]) no longer available in Canada
MEDICAL CANNABIS

CANADA:

*Nabilone* is indicated for chemotherapy-induced nausea and vomiting

Oromucosal THC–cannabidiol, *Sativex*, is conditionally approved for neuropathic pain in multiple sclerosis and cancer pain
SMOKED CB vs ORAL CB: claims made

CB claimed to be a poly-pharmaceutical herb that may provide two advantages over single-ingredient formulations

1) Therapeutic effects of the primary active CB constituents (THC) may be synergized by other compounds in CB
2) Side-effects of the primary constituents may be mitigated by other compounds (CBD, and others)
SMOKED CB vs ORAL CB: claims made

Clear advantage of smoked CB
is the rapid onset and dissipation of effects
patient is able to self-titrate the dose

*Nabilone* and *Sativex*
- more difficult for nauseous patients to consume, and more expensive than smoked CB

Vaporization is not a perfect solution since carbon monoxide is formed, but levels are significantly lower than with smoking.
MEDICAL CANNABIS

SMOKED CB vs ORAL CB:

Research funding limited due to status of THC as schedule I drug in US

More research needed to elaborate claims
As per Health Canada website (http://www.hc-sc.gc.ca/dhp-mps/marihuana/index-eng.php)

“Dried marijuana is not an approved drug or medicine in Canada. The Government of Canada does not endorse the use of marijuana, but the courts have required reasonable access to a legal source of marijuana when authorized by a physician”
MEDICAL CB REGULATIONS

After March 31, 2014, only licensed commercial producers sanctioned by Health Canada can legally grow CB.

Anyone other than a Licensed Producer who is growing CB is breaking the law and subject to law enforcement action after April 1, 2014.

Patients seeking to obtain medical CB will need to obtain a medical document from their practitioner.
MEDICAL CB REGULATIONS

Practitioners are either physicians in any provinces or territories, or nurse practitioners in provinces and territories where prescribing dried CB for medical purposes is permitted under their scope of practice.

Patient must register as a client with the licensed producer of their choice.

Amount of dried CB you can possess is the lesser of thirty times the daily amount stipulated by your health care practitioner or 150 grams.
REFERENCES


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