Recreational Cannabis: Current Safety Considerations

Lake Ontario Regional Chapter Webinar in collaboration with the Regulatory and Safety Assessment Specialty Section of SOT

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Safety Considerations:

- Acute Toxicity
- Chronic Toxicity
- Cancer
- Reproductive/Developmental Toxicity
- Impaired Driving
- Adolescents
- Vaping Lung Injuries
IDENTITY

Cannabaceae family
Genus: Cannabis
Species: Cannabis sativa, Cannabis indica, and Cannabis ruderalis

Specific plant breeding results in strains that are either high or low in THC/CBD (amongst other traits) and are grown for particular purposes (industrial hemp vs. high-THC cannabis).

Main Cannabinoids (~60 different cannabinoids, among many other constituents, including terpenes, flavanoids):

1) Cannabidiol (CBD): non-psychoactive cannabinoid.

2) Delta-9-tetrahydrocannabinol (THC): psychoactive cannabinoid (higher in flower/bud) – causes the “high”
Hemp vs. “Marijuana”

Hemp:
~20% CBD and low THC (<0.3%)
Thousands of potential uses.

“Marijuana”
Typically high THC (up to 28%) with some CBD (<5 to 15%)

THC content in plants and edibles increased from ~2% to now up to 28% (Stuyt, 2019); while concentrated products like dabs/waxes may contain as high as 75% THC.
Activity: Endocannabinoid System

THC Activity: CB1 and CB2 Receptor Agonist [inhibition of presynaptic release of several neurotransmitters including acetylcholine, L-glutamate, GABA, norepinephrine, dopamine, and 5-hydroxytryptamine (Wang, 2019)]

- Cannabinoid receptor type 1 (CB1):
  - Majority expressed in the brain (substantia nigra, globus pallidus, hippocampus, cerebral cortex, putamen, caudate, cerebellum, and amygdala)
  - Also throughout ANS/PNS (autonomic/peripheral nervous systems), including adipocytes, cardiocytes, hepatocytes, connective and musculoskeletal tissues, gonads.

- Cannabinoid receptor type 2 (CB2): Immune system cells principally, with some expression in CNS and elsewhere.

- THC direct acting while CBD when co-administered might modulate the effects of THC

Endogenous cannabinoids (endocannabinoids) have been identified and appear to have a role in pain modulation, control of movement, feeding behavior, mood, bone growth, inflammation, neuroprotection, and memory - these may be impacted by THC.
DIFFERENCES BETWEEN ORAL AND INHALED CANNABIS (THC FATE)

- Rapid absorption of THC, systemic availability following inhalation (10 to 50% bioavailability).
- Plasma $C_{\text{max}}$ and onset <5 minutes
- Maximum effect 15 to 30 minutes
- Duration 2 to 3 hours
- THC distribution to fat tissues
- Portion of THC is lost when heated.

- Slow, variable absorption following ingestion (4 to 20% bioavailability)
- Subject to first pass-metabolism 11-OH-THC (potent metabolite)
- Slower onset 30 to 90 minutes
- Maximum effect 2 to 3 hours (terminal $T_{1/2}$ of 20 to 30 hours)
- Duration 4 to 12 hours
- THC highly lipophilic - greater absorption from high fat content foods
Consumption Statistics following Legalization

Generally, the use of cannabis is rising across the continent, but even in states without legal reactional cannabis;

Some available evidence suggests:
- Use in adolescents (age 12-17): small fluctuating increases or remains stable (Williams et al., 2017; Stats Can, 2019; Cerda et al., 2017)
  - (limited data, but use is more common amongst adolescents vs. other age groups; as well as frequency).
- More clear increases in use with adults (males) and seniors (Stats Can, 2019; Hasin, 2018; Cerda, et al., 2020).

Cerda et al., (2020) found that in 12 to 17-year-olds (2008-2016) reporting cannabis use disorder (CUD) increased from 2.18% to 2.72% (a higher increase than in non-legal states), while the proportion of respondents 26 years or older reporting with CUD increased from 0.90% to 1.23% (as well as increased frequency in general).
Impact on Health Care Systems

Following legalization, spikes in hospitalizations/ER visits spike (as reported in numerous States and Canada), including acute pediatric cases/poison control calls.

- however, following the reported spikes, these appear to drop off over time,
- some increases are reported in states where cannabis is still illegal (overall prevalence and use in society),
- treatment is typically symptomatic for most cases,
- tracking data may include the use of cannabis, but not always clear if direct causal link.

Monte et al., (2019) found that of ~10,000 ED visits coded with cannabis (CO, 2012-2016), 25% were at least partially attributable to cannabis (and 10% of those were attributable to edibles).

- inhaled more attributed to hyperemesis syndrome (high frequency of visits and the greater likelihood of hospital admission) whereas edibles had higher attribution to acute psychiatric symptoms (acute anxiety or acute psychosis), intoxication, cardiovascular symptoms.
Acute Toxicity

- Cannabis use is associated with slowed reaction time, impaired attention and concentration, short term memory, and risk assessment.

- Lethal overdoses from cannabis do not occur (no respiratory depression in adults) but medical complications could trigger fatal rxn;
  - adverse effects can include tachycardia, hyper/hypotension, bronchodilation,

- Adolescents/adults: with inhaled doses of 2 to 3 mg of THC and ingested doses of 5 to 20 mg THC measured attention impairment, concentration, short-term memory and executive functioning (although highly variable) (Wang 2019).
  - Medical attention is sought typically for hyperemesis or behavioral problems (e.g., dysphoria or agitation), or other medical emergencies (bronchospasm or pneumothorax, tachycardia).

- Rare (but increasing): chest pain with myocardial infarction; ischemic stroke in young adults without any prior history (Singh et al., 2018).
Acute Toxicity

- Pediatric cases: oral doses from 5 to 300 mg have caused a range of symptoms such as mild sleepiness, ataxia, behavior changes, hyperkinesis, (Wang, 2019).

- Rare cases of seizures, coma, apnea with depressed respiration (rare but reported in pediatric and geriatric intoxication cases).
Chronic Toxicity

- Chronic smoking of cannabis can lead to adverse lung effects (NASEM, 2017):
  - symptoms such as chronic cough, phlegm production, wheeze and acute bronchitis;
  - Chronic bronchitis;
- Some evidence for elevated risks of myocardial infarction/cardiac arrhythmia, stroke (Reece, 2009; Memedovich et al., 2018; Singh et al., 2018)
Chronic Toxicity

- **Brain Effects:**
  - Animal data supports toxicity to hippocampus, amygdala, cerebellum, prefrontal cortex, and striatum; however, human data has been regionally inconsistent.

- Evidence for effects on the brain, including gray matter volume reduction in the medial temporal cortex, temporal pole, parahippocampal gyrus, insula, and orbitofrontal cortex (rich in CB1 receptors) and functionally associated with motivational, emotional, and affective processing (Battistella et al., 2014)
  - Associated with less frequent use when used in adolescents, or heavy use when unrelated to onset of use.
  - Small sample size and there is evidence that grey matter synaptic pruning occurs during adolescents (mediated by THC?).
Cancer

Although cellular data support genotoxic/carcinogenic properties, studies, including case-control, case-cohort, and systematic reviews have yielded conflicting evidence regarding the risks of various cancers associated with cannabis smoking, with most finding minimal or weak causative links.

e.g., Low evidence for **testicular germ cell tumors (10+ years of daily use)** (Ghasemiesfe et al., 2019)

- Similar compounds are created (but at higher levels in unfiltered cannabis cigarettes):
  - Benzo(a)pyrene
  - Benz(a)anthracene
  - Phenols
  - Vinyl chlorides
  - Nitrosamines
  - Reactive oxygen species

- Direct link is difficult due to:
  - Self-reported surveys of use during prohibition (under-reporting);
  - Concomitant tobacco or other drug use;
  - Strength and absolute amount of cannabis use (not just frequency);
In 2009, California’s Cancer Identification Committee (CIC) of the Office of Environmental Health Hazard Assessment (OEHHA) with Cal EPA, concluded that marijuana smoke was a carcinogen.

Evidence supporting this determination:
- Statistically significant associations with cancers of the lung, head and neck (strongest evidence), bladder, brain, and testis (certain associations also found in children with maternal/paternal exposure);
- Limitations include potential under-reporting of use, confounding due to tobacco smoke exposure etc.
- Some animal data, as well as enough mechanistic/molecular evidence (comparison to tobacco combustion).

In 2019, IARC advisory committee considered cannabis smoke a high priority future evaluation.

Developmental Toxicity

- This is an enormous topic of research that touches on many endpoints (e.g., growth, mortality, birthweight, birth defects, gestational age, immune system, neurodevelopmental/cognition).

- Concerns with broadening legalization, decreases in perceived harm potential, pregnant women may turn to cannabis for e.g., nausea (several studies reported increases in self-reported cannabis use; Fine et al., 2019; Luke et al., 2019).

- There is enough evidence (from animal and human data) to indicate concern for developmental trajectory and lasting functional consequences (Scheyer et al., 2019).

- Associations have been found for increased risk of stillbirth, small for gestational age (SGA) (<10th percentile), and spontaneous preterm birth (although may be related to confounding effects) (Luke et al., 2019).
In 2019, OEHHA (Cal EPA) concluded that there was enough evidence to conclude that marijuana smoke and THC were developmental toxins, based on a comprehensive review of available human epi data, animal studies, and molecular/mechanistic data. Note: was hazard review, not risk.

Human studies are not conclusive and subject to limitations (self-reporting, questions about dosage, potency, tobacco/drug use etc).

OEHHA will look to derive a safe exposure threshold sometime in the future.


A great deal more research is required in this area.
Reproductive Toxicity

- Cannabinoid receptors found in the hypothalamus, pituitary, endometrium (CB1), ovary/testes (CB1 + CB2), and spermatozoa (CB1+CB2) (Dunne, 2019)

- In vitro/animal studies suggest that THC can:
  - Impair HPO function, interfere with ovulation, suppress hormone levels (GnRH, FSH, and LH),
  - Adversely effect sperm motility and sperm fertilization.

- Available fertility studies in humans have not found an association,

- A few clinical evaluations have not found associations between cannabis use and testosterone production, sperm motility, and fertility potential in male users.
Does cannabis impair driving ability?

- Substantial evidence of increased THC-positive blood samples in car-crash fatalities (but presence in blood does not mean impairment at time of crash).

- Sufficient evidence of impairment in simulations (lane weaving, decreased reaction times, slower driving) (Brubacher, 2011) (Pumell and Howell, 2018).

Lane and Hall (2019): increase of 1.08 traffic fatalities per million residents (CO, Washington, Oregon) in the year following recreational cannabis legalization followed by a return to baseline (including for neighboring, non-legalizing states).

- Return to baseline also reported by Leyton (2019)
Impaired Driving/Fatalities

- The results are mixed: trying to link, national/state-level statistics regarding increasing in crashes,
- Aydellote et al (2019): increase in crash rates in CO+Washington (stronger correlation with opening of dispensaries)
  - Aydellote et al. (2017); Hansen et al., (2018) – no statistically significant effects in Washington and CO.
- Anderson et al (2013) found an 8 to 11% decrease in traffic fatalities following legalization (possible substitution effect with alcohol/less impairing than alcohol).
- NASEM (2017): substantial evidence of statistical association for increased risk of motor vehicle crashes (but study limitations re: actual impairment unclear).
### Adolescents

Current evidence and areas of research with heavy adolescent cannabis use (Grewal and George, 2017; CCSUA, 2014):

- Elevated risk of dependence and use disorder later in life,
- Associated with increased risk of experiencing psychotic symptoms, onset of first psychotic episode in adulthood, or being diagnosed with schizophrenia later in life (genetic and pre-existing vulnerabilities play an important role).
- Attention, memory, and verbal learning,
- Decreased IQ scores (debatable),
- Concerns with impaired risk assessment and impaired driving.

Does drug use induce mental illness? Or does mental illness increase risk for drug use?
Adolescents

- Gobbi et al., 2019.
- 11 studies comprising 23,317 individuals.
- Cannabis use prior to 18 years of age and then mental health at 18 to 32 years of age.

- Depression: 1.37 (95% CI, 1.16-1.62)
- Suicidal ideation: 1.50 (95% CI, 1.11-2.03)
- Suicidal attempt: 3.46 (95% CI, 1.53-7.84)
- Anxiety: no significant association.
As of Feb. 18, 2020 (CDC, 2020):

- Acute respiratory issues (coughing, shortness of breath, chest pain), fever, emesis, and radiological imaging patterns consistent with lipoid pneumonia, eosinophilic pneumonia, ground glass opacities, and chemical damage to the lung tissue.

- **2,807** hospitalizations/deaths across all 50 states (68 deaths).

- Some evidence suggests it is vitamin E acetate (VEA) found in THC-containing e-cigs (CDC, 2020).

- Identified in bronchoalveolar lavage (BAL) fluid samples of 48 of 51 cases (none found in healthy comparison group);

- No other toxicants found in BAL samples.
Muthumalage et al., (2020) compared counterfeit/consumer-provided THC vape products to medical-grade cartridges (via GCMS):

- Vitamin E acetate was detected in counterfeit cartridges but not in all cases.
- Other constituents found that may be involved in lung injury include:
  - solvent-derived hydrocarbons,
  - silicon conjugated compounds,
  - various terpenes,
  - pesticides/plasticizers/polycaprolactones, and
  - metals (most abundant: Si, Cu, Ni, and Pb).
Summary/Conclusions

Legalization of recreational cannabis:

1) Some evidence indicates slight increase in overall consumption....
   - Adolescents: slight increases or stable, but use highly prevalent in this population!
     - (but not participating in regulated market!)
   - Increase in first-time users, increases in consumption among older males and seniors.
   - Evidence to suggest there are increases in CUD (adolescents and adults).

2) Increases in hospitalizations/ER visits in Canada and US:
   - Evidence supports that spikes do occur (but may taper off)
   - Pediatric cases are particularly concerning.
3) Cannabis-related motor vehicle fatalities

- There are statistical associations with cannabis use and increased car crashes; however, data is inconsistent; some evidence for return to baseline or even decreases.

- Some suggestions for possible substitutional effect with alcohol (and decreases in fatal crashes).
Summary/Conclusions

4) Toxicity Endpoints

- Acute overdose
  - are generally symptomatic/supportive, although severe effects do occur (cardiovascular)
  - Pediatric cases are more severe and can include coma/seizures

- Chronic Toxicity
  - primarily related to lung effects, although cardiovascular effects also reported.

- Cancer: no substantial causal link yet (study limitations), but combustion by-products comparable to cigarettes and are generally inhaled unfiltered and more deeply.

- Developmental Effects: sufficient evidence to warrant avoidance, additional research needed to pinpoint specific endpoints (currently data points to low birth weights)

- Reproductive Effects: mechanistic/animal data indicates potential for adverse effects in males an females, although clinical data (limited) has not found any associations.
Summary/Conclusions

5) Adolescents:
- Data indicates heavy daily use in adolescence associated with (predisposing conditions hard to decipher):
  - increased odds of later cannabis dependence/increase use,
  - suicide attempt/ideation,
  - Earlier onset of 1st psychotic episodes/psychotic episodes,
  - Depression.

6) EVALI: appears to be associated with counterfeit/street cartridges that contain vitamin E acetate or potential various other compounds (chemical pneumonitis).
Summary/Conclusions

- Limitations in existing research:
  - Controlling for confounding factors, where possible (tobacco, pre-existing/undiagnosed mental health conditions and genetic predisposition cannot always be accounted for but may play a critical role in adverse effects associated with cannabis use/misuse, especially in adolescents)
  - Unified approach to quantifying cannabis use re: frequency, dosage, potency.
References

https://calgaryherald.com/cannabis/cannabis-health/cannabis-related-hospital-visits-spike-since-legalization-physicians
References

- Battistella et al., (2014): https://www.nature.com/articles/npp201467