The current evidence of benefits and risks pertaining to the use of marijuana and its derivatives, both medically and recreationally.

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The speaker has no relevant financial relationship(s) to disclose.
Introduction

• Reason for addressing this topic: We are surrounded by states with legalized medicinal and recreational marijuana and its derivatives.
  – Many in Idaho are using these substances, though they remain illegal here. While illegality is an obvious issue, how else should patients be counseled, from an evidence based standpoint?
  – Could these substances be beneficial for certain patients? Are there severe risks to be mindful of? What are the reasons patients are using, and is there evidence supporting why they use?
Legalization of Marijuana

• States with legalized recreational use (laws vary by state regarding possession, growth, distribution, etc.):
  – 33 states and D.C. with medical legalization.
  – Federally, the DEA classifies marijuana as a schedule I drug: no current acceptable medical use, and a high potential for abuse. It is illegal under federal law. CBD sourced from Hemp plants is legal to produce.

• common/societal perception: that marijuana is harmless when used recreationally and is an excellent medical treatment for many conditions.

• Risks are often not discussed in media, may be unknown to users.

• Poor regulation of marketing.
Basics

• Genus *Cannabis*, various species, most commonly *sativa* species.

• *Cannabis* has been used for its medicinal and psychotropic properties for thousands of years.

• Has been used medicinally for years, dating back to ancient civilizations (more than 5,000 years). Used medicinally in the US in the 19th and early 20th centuries.
Endocannabinoid System

• Endocannabinoid system: throughout the CNS and PNS, also other tissues. Involved in homeostasis of various systems, sleep, concentration, memory, reward, cognition, pleasure, appetite, stress response/reduction, and modulation of pain and inflammation.

• also noted to affect neuronal development in animal studies.

• Cannabinoid receptors discovered in 1980s (CB1 and CB2). Most prevalent and concentrated in neural tissues, especially in the hippocampus, cerebellum, amygdala, and prefrontal cortex, but also present throughout the body.
Phytocannabinoids

• The active substances in *Cannabis sativa* plants.
• >420 chemical compounds in *Cannabis* plant. 61 are cannabinoids.
• More than 150 known compounds in *Cannabis* smoke.
• Most commonly known/studied cannabinoids are delta-9 Tetrahydrocannabinol (THC) and Cannabidiol (CBD).
  – THC: Primary psychoactive substance. THC content in Cannabis plants increasing over last 30 years.
  – CBD: complexes differently than THC with cannabinoid receptor and does not have the same psychotropic activity.
How is *Cannabis sativa* being used?

- Various formulations and methods of intake: smoked, edible, oils, tinctures, oral whole plant extract, nabiximols (CBD-THC purified mixture)
  - Nabiximols (oral spray) is approved for use in Canada and the UK as an analgesic and muscle relaxant
- Synthetics: dronabinol (oral synthetic THC solution or capsule), nabilone (synthetic cannabinoid compound oral capsule), Epidiolex (oral CBD solution)
  - dronabinol is FDA approved chemotherapy induced nausea and vomiting, and appetite stimulation in HIV/AIDS.
  - nabilone is FDA approved for severe, refractory nausea and vomiting
  - Epidiolex is FDA approved for refractory seizure syndromes
- Hemp: *Cannabis* that contains no more than 0.3% THC.
  - For industrial uses such as textiles, food and cosmetic products, and building materials.
https://fivethirtyeight.com/features/marijuana-edibles-are-a-gamble-for-users/

Timing and effects

• Approximately 2 to 3 mg of inhaled THC is sufficient to produce drug effects in a naïve user. How much per inhalation depends on strain of Cannabis used.
  – Onset of psychoactive effects occurs rapidly with peak effects felt at 5 to 30 minutes and lasting up to four hours
• Cannabis ingestion has a delayed onset of psychoactive effects that ranges from 30 minutes to three hours. Clinical effects may last up to 12 hours
  – In naïve users, psychotropic effects occur with 5 to 20 mg of ingested THC
  – Most prepackaged edible products contain about 4x the recommended dose per use of 10 mg THC.
• Oromucosal route produces effects in 15-45 minutes with a duration of 6-8 hours
• Appropriate or effective amount of a given formulation to use, to achieve a desired effect, is unclear and vary with the strain used, especially when THC content of typical available recreation products ranges from 5-20%.
Discussion of benefits and risks of use of *Cannabis* and cannabinoids

- The following is based primarily on the NASEM report regarding the therapeutic affects of *Cannabis* and cannabinoids, published January 2018, the 2018 WHO report on the effects of nonmedical cannabis use, and the 2019 AAFP position paper.
Benefits

• Chronic Pain:
  • Limited and mixed evidence.
  • 5 fair to good systematic reviews. One review with 28 RCTs found cannabinoids to be beneficial in alleviating chronic pain. Most of these trials investigated whole plant extract, nabiximol, 5 looked at smoked or vaporized Cannabis plant material.
  • 17 of the trials looked at neuropathic pain alone.
  • NASEM concluded no conclusive or substantial benefit.
  • Most studies did generally suggest improved pain control (up to 30-40%) reduction in pain vs control, but most of these generally failed to reach statistical significance.
  • Recent open-label study of medicinal cannabis for patients with chronic pain showed improvement in pain, but also 44% of those on opioids had discontinued their opioids at the end of the 6 month study period. (Fitzcharles). No discussion on QOL or adverse effects, though.
  • Large amount of observational studies reporting patient satisfaction with cannabinoid treatments.
Benefits

• Chemotherapy Induced Nausea and Vomiting:
• Most studies look at dronabinol and nabilone.
• In adults these are highly effective. Better than placebo, and similar to conventional antiemetics.
  – Rates of adverse effects higher, but still preferred by patients over other antiemetics. Results in peds not as conclusive.

• No good studies in literature looking at whole plant *Cannabis* or CBD extract. Lots of anecdotal evidence.
Benefits

• MS related spasticity:
  • Mixed evidence, without statistical significance, looking at benefit of variable doses of THC and CBD.
  • Pooled analysis of 3 trials evaluating nabiximol or nabilone vs placebo. Found to improve patient self-reported spasticity scores. Results were statistically significant.
    – When Ashworth scores were evaluated in different pooled analysis of 5 studies, score improvements were found vs placebo, but not statistically significant.
Limited evidence for benefit: mixed findings, uncertainty, high amount of bias or confounders in studies

• Appetite stimulation and weight gain, PTSD treatment, anxiety treatment, Tourette syndrome treatment
Inconclusive in determining benefit: due to mixed findings, poor studies, lack of data.

- Treatment of psychiatric disorders, cancer curative treatment, Epilepsy treatment (as a whole), treatment of neurodegenerative disorders (Huntington’s, Parkinson’s, ALS, etc), treatment of IBS, addiction therapy (primarily opioid and nicotine).
Benefits

• In treatment resistant epilepsy (primarily Dravet syndrome and Lennox-Gastaut), CBD has shown some benefit for seizure control as an adjunctive medication to traditional antiepileptics. No evidence available with CBD as sole treatment. Most studies reported fatigue and somnolence as main adverse effects.
Summary of Benefits

• Some modest benefits, studied and noted mostly with purified extracts and current FDA approved formulations. Severe need for more high quality studies to get a better understanding of whole plant marijuana effects.

• There is concern regarding medical use of marijuana, since it has not undergone the same FDA scrutiny, regulation, and approval that most drugs have.
Risks of use of *Cannabis* and its derivatives
Risks

• Intoxication/side effects (or intended effects) of use:
  Euphoria, tachycardia, tachypnea, hypertension, dry mouth, nystagmus, ataxia, increased appetite, slurred speech, dizziness, tiredness, short term cognitive impairment persisting even 24 hours after use, psychosis/hallucinations. Some will experience dysphoria, anxiety, or panic.

• Acute use of Cannabis results in impairment of every important metric related to the safe operation of a motor vehicle. Multiple studies demonstrate increased risk for MVA with acute marijuana intoxication.
Risks

• Dosing and effect is difficult to determine in recreationally available products. There are no well-demarcated levels of how dosages may affect an individual, thus one easily may ingest or use more than intended.
  – Extremely high doses are needed to cause severe adverse effects
  – Per 2018 WHO report:
    • The risk of a fatal cannabis overdose is extremely small. The dose of THC that would be a fatal dose in humans, extrapolated from animal studies, is between 15 g and 70 g.
Risks

• Some edibles are difficult to distinguish from normal foods and candies.

• Overdoses in children who have ingested products: sleepiness, euphoria, irritability, delirium, slurred speech, depressed mental status. Coma with apnea, or depressed respiratory status in large overdoses (typically seen at extremely high doses, around 300 mg THC).

• Pediatric exposures occur more frequently in states with legalized recreational use.
Risks

- Respiratory Diseases: mainly occur with smoked (and possibly vaporized) products.
- COPD: small amount of evidence for increased risk after controlling for tobacco use.
- Asthma: no association for development of asthma. Certainly could trigger.
- Bronchitis, general respiratory symptoms: Long term Cannabis smoking causes symptoms of bronchitis and microscopic injury to bronchial lining cells, leading to lung scarring. There is moderate evidence for improvement in symptoms such as cough and phlegm after cessation.
- Lung cancer: at this time, it is unclear from the current evidence if smoking marijuana is a risk factor
Risks

• CV Risk:

• Evidence examining the effect of marijuana on cardiovascular risk factors and outcomes, including stroke and myocardial infarction, is insufficient. (Ravi)

• WHO report states some evidence for intoxication triggered events.

• Long term heavy use potentially triggers stroke and MIs in young users (<50 years old).
Risks

• Psychosocial:
  • Cognitive deficits with acute use. Impaired learning, memory, and attention related to recent cannabis use, even as long ago as 24 hours. Decrease motivation during intoxication.
  • Increasing evidence that these deficits persist even beyond the initial 24 hours.
  • Effect probably decreases after 72 hours abstinence.
  • In adolescents that use marijuana there is a negative impact on educational attainment, lifetime achievement in employment, income, and social relationships and roles. (Fitzcharles)
Risks

- Mental Health and Substance Abuse:
- 9% of users will develop addiction, more likely with earlier use (17% risk of addiction if using as teenager, 25-50% risk if using daily as a teen).
- Acute psychotic episodes with acute use. These are becoming more frequent, related to increasing THC concentrations.
- Increased risk of schizophrenia, especially when use initiated at a young age, and frequent users.
- Likely increased risk for social anxiety disorder
- Associated with development of suicidal thoughts, causality not established
- Cannabis use associated with increased risk for abuse of other substances.
  - In one study, approximately 1/4 of chronic pain patients using medical cannabis were high risk alcohol drinkers.
Risks

• Prenatal, perinatal, neonatal risks:

• Some dispensaries in Colorado were found to be recommending *Cannabis* products for morning sickness treatment. Most recommending edibles.
  – Unregulated employee training and no regulations about recommendations or advice that employees can give.
  – Studies have shown that only around 20% of dispensary employees have some sort or medical or scientific training. 71% of employees giving advice based it on personal experience only.
Risks

• Prenatal, perinatal, neonatal risks:
• Preterm birth and low birth weight
• Later in life, children show: impaired attention, learning, and memory; impulsivity and behavioral problems; higher likelihood of using marijuana as an adult
• Just released study by Baker, et al, shows that newborns who are exclusively breast fed will ingest about 2.5% of the THC that the mother takes in when using marijuana (primary method was smoking). THC remains in breast milk up to 6 days. Unfortunately, the long term affects of this are still poorly understood.
Risks

- Cannabis Use Disorder: Specific DSM-V diagnosis, similar to other substance use disorders.
  
  - A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

  1. Cannabis is often taken in larger amounts or for a longer period than was intended.
  2. There is a persistent desire or unsuccessful efforts to cut down or control cannabis use.
  3. A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.
  4. Craving, or a strong desire or urge to use cannabis.
  5. Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home.
  6. Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.
  7. Important social, occupational, or recreational activities are given up or reduced because of cannabis use.
  8. Recurrent cannabis use in situations in which it is physically hazardous.
  9. Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis.
  10. Tolerance, as defined by either of the following:
    - a. A need for markedly increased amounts of cannabis to achieve intoxication or desired effect.
    - b. Markedly diminished effect with continued use of the same amount of cannabis.
  11. Withdrawal, as manifested by either of the following:
    - a. The characteristic withdrawal syndrome for cannabis.
    - b. Cannabis (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.
Risks

• Cannabis withdrawal syndrome:
  – constellation of signs and symptoms occurring within 1 week after abrupt reduction or cessation of heavy or prolonged Cannabis use. Irritability, anger, anxiety, depression, sleep disturbances, abdominal discomfort, headache, muscle tremor, or muscle twitching.
Risks

• Cannabis Hyperemesis Syndrome.
  – Cyclic vomiting-like condition associated with long term and high dose cannabis use. Those affected self-treat with repetitive hot water bathing behavior during vomiting cycles.
Opioids and *Cannabis*

- Effects of concomitant THC and opioid use:
  - Shared effects: antinociception/analgesia, hypothermia, inhibition of locomotor activity, hypotension, sedation
  - THC enhances the effects of opioids
    - THC has some action at opioid receptors
    - THC stimulates the release of endogenous opioids
    - THC enhances the acute analgesic effect of opioids
- Side effects are additive. Increased severe adverse events.
- In patients using opioids and *Cannabis*, serious adverse events are as high as 20/100 patient-years.
- Study of *Cannabis* plus opioids: 44% of those on opioids had discontinued their opioids at the end of the 6 month study period.
Position statements

• AAFP

Medical Use of (2016)
• The AAFP recognizes that there is support for the medical use of marijuana but advocates that usage be based on high quality, patient-centered, evidence-based research and advocates for further studies into the use of medical marijuana and related compounds. The AAFP requests that the Food and Drug Administration change marijuana’s classification for the purpose of facilitating clinical research. This process should also ensure that funding be available for such research.
• The AAFP also recognizes that some states have passed laws approving the medical use of marijuana; the AAFP does not endorse such laws. The AAFP encourages its members to be knowledgeable of the laws of their states and consult with their state medical boards for guidance regarding the use of medical marijuana.

Recreational Use of (2019)
• The American Academy of Family Physicians (AAFP) opposes the recreational use of marijuana. However, the AAFP supports decriminalization of possession of marijuana for personal use. The AAFP recognizes the benefits of intervention and treatment for the recreational use of marijuana, in lieu of incarceration, for all individuals, including youth.
• The AAFP also recognizes that several states have passed laws approving limited recreational use and/or possession of marijuana. Therefore, the AAFP advocates for further research into the overall safety and health effects of recreational use, as well as the effects of those laws on patient and societal health.
Position statements

• ACOG (2017)
  • The American College of Obstetricians and Gynecologists recommends the following:
    – Before pregnancy and in early pregnancy, all women should be asked about their use of tobacco, alcohol, and other drugs, including marijuana and other medications used for nonmedical reasons.
    – Women reporting marijuana use should be counseled about concerns regarding potential adverse health consequences of continued use during pregnancy.
    – **Women who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use.**
    – Pregnant women or women contemplating pregnancy should be encouraged to discontinue use of marijuana for medicinal purposes in favor of an alternative therapy for which there are better pregnancy-specific safety data.
    – There are insufficient data to evaluate the effects of marijuana use on infants during lactation and breastfeeding, and in the absence of such data, marijuana use is discouraged.
Summary

• Complex system with many exogenous cannabinoids from Cannabis plants. Many ways that these products are being used. Multitude of dosage forms, dosages not well understood or standardized.

• Some evidence possibly for management of pain, nausea and vomiting, MS related spasticity, epilepsy syndromes.

• Lots of risks, poor understanding of whole plant effects, poor understanding of effects from most common ways of use.
Needs for further study

• The list goes on and on...
How to counsel patients

- Evidence for benefits from *Cannabis* limited, poorly understood.
- Lots of side effects of use, especially with whole plant material. Possibly long term detrimental effects.
- Not a replacement for opioids, still plenty of side effects, risk for addiction and use disorder. Avoid using marijuana+opioids, benzos, or other controlled substances.
- Probably better treatment options for many of the conditions for which patients may want to use *Cannabis*, at this time.
- A last resort for most things
- Still illegal in Idaho, can’t protect the patient from law enforcement if using illegally. Best not to risk it.
Amusing yet concerning...

Obstetrics: Original Research

Recommendations From Cannabis Dispensaries About First-Trimester Cannabis Use

Betty Dickson, sto, Chandel Mansfield, sso, MARYam Ghassemi, NDO, Amanda A. Albright, MS, Lauren M. Bargell, Ms, Joanne Shroder, Mh, Robert M. Silver, MD, and Torri D. Metz, MD, MS

OBSERVATIONAL STUDY

OBJECTIVE: To characterize recommendations given to pregnant women by Colorado cannabis dispensaries regarding use of cannabis products for nausea during the first trimester of pregnancy.

METHODS: This was a state-wide cross-sectional study in which advice about cannabis products used by pregnant women was surveyed using a single, anonymous questionnaire. Dispensaries were randomly selected from the Colorado Department of Revenue Enforcement Division website. The primary outcome was the proportion of dispensaries that recommended cannabis for nausea during pregnancy. We hypothesized that 50% of dispensaries would recommend it. A sample size of 400 was targeted to yield a two-sided 90% CI width of 10%.

RESULTS: Of the 467 cannabis dispensaries that were licensed in Colorado, 391 were licensed for medical use (n = 348), 25% for retail (n = 111), and 30% for both (n = 151). The majority (84%) (377/460) recommended treatment of morning sickness with cannabis products (45% CI 66-73%).

CONCLUSION: Nearly 70% of Colorado cannabis dispensaries contacted recommended cannabis products to treat nausea in the first trimester. Few dispensaries mentioned a recommendation was not based on scientific evidence and that there is no regulatory standard for cannabis.
Amusing, yet concerning…

• Excerpts from Colorado study regarding 1st trimester advice from dispensaries:
  • “I’m calling because I’m 8 weeks pregnant and nauseated. Are there any products that are recommended for morning sickness?”
    – “Let me call my daughter, she just had a baby, call me back in 5 minutes.”

• Why is the product recommended or not recommended?
  – “Edibles would not hurt the child; they would be going through your digestive tract.”

• Responses regarding speaking with a health care provider
  – “The doctor will probably just tell you that ‘marijuana is bad for kids and will just try pushing pills on you.’ Maybe you have a progressive doctor that will not lie to you. All the studies done back in the day were just propaganda.”
  – “Google it first. Then if you feel apprehensive about it, you could ask.”
  – “Most of them out here tell them not to smoke weed. Even the cancer doctors. It is so messed up. I do not know how the baby doctors work, if they are chill or not. Just do not go stoned when you talk to them.”
  – “No, because they will test you when the baby is born and can get child protective services involved; that is just the unfortunate honest truth.”
Questions?
References

1. AAFP Policy Statement on Marijuana. [AAFP.org](http://www.AAFP.org) 2016
RESOURCES FROM TODAY’S SESSION AND PAST SESSIONS CAN BE FOUND IN OUR ONGOING RESOURCE LIST.

https://iecho.unm.edu/sites/uidaho/download.hns?i=51