“MEDICAL” MARIJUANA: WHAT’S THE EVIDENCE?

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OBJECTIVES:

- To review definitions and terms related to the cannabis plant and its products.
- Discuss current evidence available regarding potential medical efficacy of cannabis-derived materials.
- Outline the risks and adverse effects of these products.
• **Cannabis** - collective term referring to the genus of flowering plant in the family *Cannabaceae*.
  - The *Cannabis* genus (species *sativa* and *indica*) produces more than 60 chemicals (C21 group) called Cannabinoids.

• **Marijuana** - is the common name for a mixture of dried leaves and flowers of the female *C. sativa* plant.

• **Hemp** is a different variety of *C. sativa*:
  - The term *hemp* is used to name the durable soft fiber from the *Cannabis* plant stem(stalk). *Cannabis sativa* cultivars are used for fibers due to their long stems; Sativa varieties may grow more than six meters tall. However, *hemp* can refer to any industrial or foodstuff product that is not intended for use as a drug. Many countries regulate limits for psychoactive compound (THC) concentrations in products labeled as hemp.

• **Hashish and hashish oil** are the pressed resin and the oil expressed from the pressed resin.
DEFINITIONS

• “Cannabinoid” refers to compounds that bind to and agonize the cannabinoid receptors
  • Phytocannabinoids-derived from the Cannabis plants
  • SCRA- “Synthetic Cannabinoid Receptor Agonists” (K2, “Spice,” but also Nabilone (Cesamet)® and Dronabinol (Marinol®))
  • Endocannabinoids- endogenously existing neuromodulators (2-archidonoylglycerol (2-AG) and anandamide)

• The major cannabinoids are cannabidiol (CBD), and tetrahydrocannabinol (THC).
  • THC, or Δ⁹-tetrahydrocannabinol is the principal psychoactive cannabinoid.
  • Cannabidiol does not have the intoxicating properties of THC, but does have some activity at the CB1 and CB2 receptors.
    • Has anti-oxidant and anti-inflammatory properties
  • THC and Cannabidiol are related by a common precursor, and strains Cannabis are derived to express either a majority of one or the other, or a mixture of both.
    • “CBD” strains for industrial hemp cannot contain more than 0.3 % Δ⁹-THC
    • Strains engineered for recreational use try to preferentially have higher THC content.
SYNTHESIS:
THC CONCENTRATIONS

• “Low Grade” – 1-5%
• “High Grade” – 10-25%
• Hash, Hashish Oil – up to 50%
• Dabs, Shatter, Concentrations – up to 97%
The Health Effects of Cannabis and Cannabinoids
THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH
16 Experts in areas of marijuana, addiction, oncology, cardiology, neurodevelopment, respiratory disease, pediatric and adolescent health, toxicology, research, epidemiology, immunology and public health, who were asked to

1. Develop a comprehensive review of existing evidence regarding the health effects of using marijuana
2. Make recommendations for a research agenda regarding the association of cannabis and health outcomes (harm and benefit)
SUMMARY OF REPORT

• Identified >24000 published reports
  • Removed non-English, case reports, conference abstracts, etc.
  • Left with 10,700, from which they prioritized and reported on:
    • Health Outcomes (variety of disease states)
    • Risks of Cancer, Cardio-metabolic and Respiratory Disease
    • Effects on Immunity, Injury/Death
    • Prenatal/Perinatal Exposure, Psychosocial, Mental Health, Cannabis Use Disorders, Cannabis use and use of other substances
EVIDENCE CATEGORIES

- **Conclusive** - Strong evidence from RCTs
  - No Strong Opposing Evidence, Many Findings

- **Substantial** - Strong evidence
  - Good Quality Studies, Several Findings

- **Moderate** - Some Evidence
  - Good/Fair Quality Studies, Some Findings

- **Limited** - Weak Evidence
  - Fair Quality or Mixed Findings

- **No/Insufficient Evidence**
  - Poor Studies, Mixed Findings or Nothing
THERAPEUTIC EFFECTS

- Conclusive/Substantial Evidence:
  - Cannabis effective for Adult Cancer Pain
  - Oral Cannabinoids Effective for
    - Anti-emetics in Cancer-Induced Nausea and Vomiting (CINV)
  - Patient-reported spasticity symptoms in MS
THERAPEUTIC EFFECTS

• Moderate Evidence
  • Cannabinoids, primarily Nabiximols, can improve short term sleep outcomes in individuals with sleep disturbances as a result of OSA, fibromyalgia, chronic pain and MS
  • Nabiximols: THC/CBD compounds in an oromucosal spray
THERAPEUTIC EFFECTS

• Limited evidence
  • Cannabis and Oral Cannabinoids improve appetite and decrease weight loss in HIV/AIDS
  • Oral Cannabinoids: Improving clinician-measured spasticity in MS
  • THC Capsules improve Tourette Syndrome
  • Improving anxiety symptoms in individuals with social anxiety disorders (cannabidiol)
  • Nabilone: improving PTSD symptoms
    • One single, small, fair-quality trial
THERAPEUTIC EFFECTS

• Limited Evidence, continued:

  • Statistical association between cannabinoids and better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage

  • Cannabis use is *ineffective* for:
    
    • Glaucoma
    
    • Dementia symptoms
    
    • Depression symptoms in chronic pain and MS
THERAPEUTIC EFFECTS

- No or Insufficient Evidence
  - Cancers
  - Cancer-associated cachexia syndrome
  - Anorexia nervosa
  - Irritable bowel syndrome
  - Epilepsy
  - Spasticity due to spinal cord injury
  - Symptoms of ALS, Huntington’s or Parkinson’s
  - Dystonia
  - Addiction
  - Schizophrenia
DOES IT CAUSE CANCER?...

- **Moderate evidence** that there is **no** association between smoking cannabis and lung cancer or head/neck cancers
- **Limited evidence** of association between smoking cannabis and non-seminoma testicular germ cell tumors
- **No evidence** to support/refute associations with:
  - Incidence of esophageal cancer (cannabis smoking)
  - Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi’s sarcoma, or bladder cancer
  - Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use)
OTHER RISKS

• **Cardiac:**
  
  • **Limited evidence** of a statistical association between cannabis use and:
    
    • Triggering an acute MI (cannabis smoking) (6-1a)
    • Ischemic stroke or subarachnoid hemorrhage (6-2)
  
  • **Insufficient evidence** for association between chronic use and risk of MI.
OTHER RISKS

• **Metabolic:**
  • Limited Evidence for a statistical relationship between cannabis and:
    • Decreased risk of DM and metabolic syndrome
    • Increased risk of prediabetes
OTHER RISKS

• **Respiratory:**

  • **Substantial evidence** of a statistical association between cannabis smoking and:
    • Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking)

  • **Moderate evidence** of a statistical association between cannabis smoking and:
    • Improved airway dynamics with acute use, but not with chronic use
    • Higher forced vital capacity (FVC)

  • **Moderate evidence** of a statistical association between the **cessation** of cannabis smoking and improvements in respiratory symptoms

• **Limited evidence** of a statistical association between cannabis smoking and:
  • An increased risk of developing chronic obstructive pulmonary disease when controlled for tobacco use (occasional cannabis smoking)

• **No or insufficient evidence** to support or refute a statistical association between cannabis smoking and:
  • Hospital admissions for COPD
  • Asthma development or asthma exacerbation
OTHER RISKS

- **Substantial Evidence**
  - Increased risk of MVA

- **Moderate Evidence**
  - Increased risk of overdose in pediatric patients where cannabis is legal

- **No/Insufficient Evidence**
  - All-cause mortality (self-reported cannabis use)
  - Occupational accidents or injuries (general, non-medical cannabis use)
  - Death due to cannabis overdose
NEONATAL/PERINATAL RISKS

- **Substantial Evidence**
  - Maternal use and lower birth weight
- **Limited evidence**
  - Maternal Pregnancy complications
  - NICU Admission
- **Insufficient Evidence**
  - Later outcomes in offspring (SIDS, cognitive, etc.)
PSYCHOSOCIAL RISK

• **Moderate evidence**
  - Impairment of learning, memory and attention
    - Acute use

• **Limited evidence**
  - Impaired academic achievement
  - Impaired social functioning
  - Increased unemployment/ low SES
  - Sustained abstinence and cognitive impairments
MENTAL HEALTH

• **Substantial Evidence**
  - Development of schizophrenia or other psychoses
    - Highest in most frequent users

• **Moderate Evidence**
  - Cognitive performance improvement in individuals with psychotic disorders and a history of cannabis use.
  - Increased symptoms of mania and hypomania in bipolar patients with regular cannabis use.
  - Small increase in risk of developing depressive symptoms
  - Increased incidence of SI, suicide attempts and *completed* suicide
  - Increased likelihood of social anxiety disorder
MENTAL HEALTH

• **Moderate Evidence**
  - NO worsening of *negative* schizophrenia symptoms

• **Limited Evidence**
  - Increase in *positive* schizophrenia symptoms
  - Likelihood of developing bipolar disorder increased
  - Increased anxiety symptoms or developing anxiety disorder (other than social anxiety)
  - Increased severity of PTSD symptoms

• **No Evidence**
  - Changes in course of depressive symptoms
  - Development of PTSD
PROBLEM CANNABIS USE EVIDENCE

- “the experience of persistent or recurrent social, interpersonal, occupational, academic, recreational, psychological, or physical problems caused or exacerbated by cannabis use”

- **Substantial**
  - Stimulant treatment of ADHD is not a risk factor
  - Male and smoking cigarettes are risk factors
  - Initiation at younger ages is a risk factor
  - Increased frequency of cannabis use is associated
  - Being males is associated with increased risk of the severity of problem use
    - Recurrence is the same as female
• Moderate Evidence Regarding Development of Problem Cannabis Use:
  • Anxiety, personality and bipolar disorders, and adolescent ADHD are *not* risk factors
  • Major Depressive disorder is a risk factor
  • Being male is a risk factor.
  • Exposure to combined use of abused drugs is risk factor
  • Neither alcohol or nicotine dependence alone are risk factors for problem cannabis use.
  • Use During adolescence- the following are risk factors: Frequency of use, oppositional behaviors, age of 1st alcohol use, nicotine use, parental substance use, poor school performance, antisocial disorders and sex abuse
  • A persistence of problem cannabis use and a history of psychiatric treatment
  • Problem cannabis use and increased severity of PTSD symptoms
• Limited
  • Childhood anxiety and childhood depressive are risk factors
OTHER SUBSTANCE ABUSE

- **Moderate evidence** linking cannabis use to the development of other substance dependence or substance use disorders
  - Alcohol, nicotine, illicit drugs

- **Limited evidence**
  - Cannabis use changes rates or use patterns of other substances
  - Initiation of tobacco use
CANNABINOID HYPEREMESIS SYNDROME

- Syndrome of abdominal discomfort, nausea and hyperemesis following chronic, heavy marijuana use
  - Symptoms refractory to opioids and anti-emetics.
  - Hallmark-immediate relief of symptoms with bathing or showering in hot water, and a major diagnostic feature is compulsive bathing.
- Unclear pathophysiology
  - Hot water relief indicates dysfunction of pain perception, excess substance P release, and activation of TRPV1
  - Ultimately, successful treatment is cessation of marijuana use
SUMMARY:

• In summary, our knowledge of the benefits and risks of marijuana is limited by a lack of research.
• FDA is currently conducting some studies on cannabidiol derivatives for conditions such as epilepsy.
• There are very few scenarios where there is actually evidence that marijuana is helpful, and most of them are palliative.
• That does not allow for a strong risk/benefit ratio for many of those seeking a “recommendation” for marijuana.
REFERENCES

• Douglas C. Throckmorton, M.D. “FDA Regulation of Marijuana: Past Actions, Future Plans” Presented at Food and Drug Administration (FDA) ICSB/ASP Joint Meeting; April 12, 2016

