



# “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.

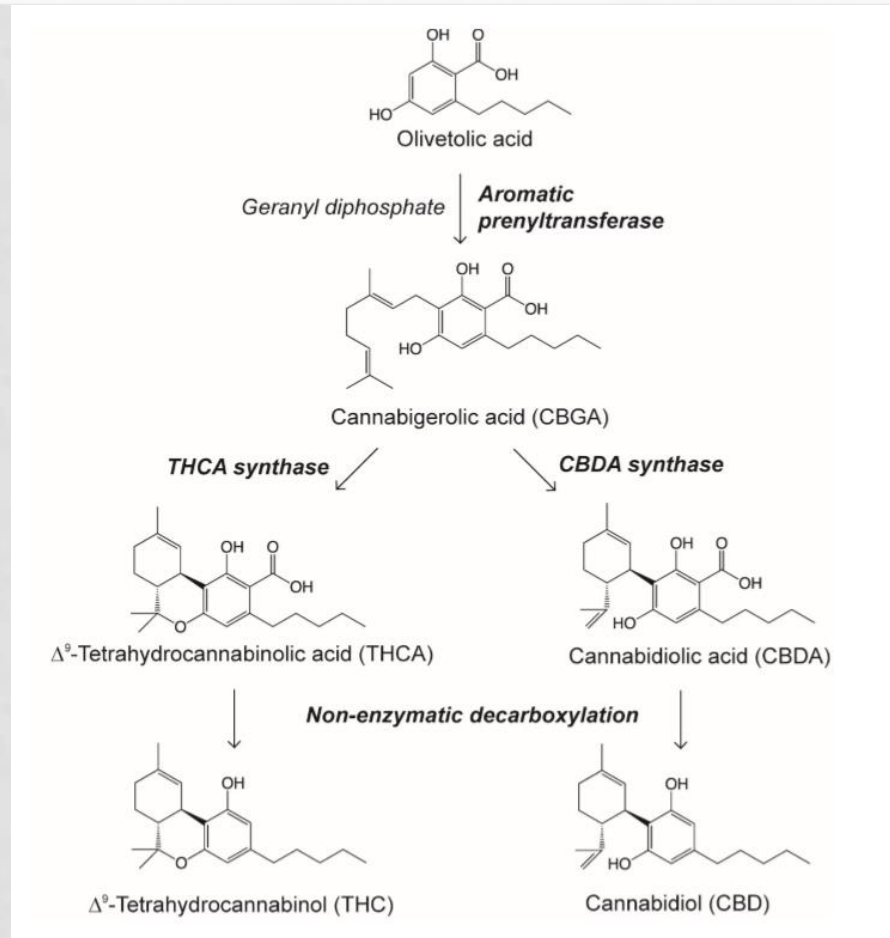
# DEFINITIONS

- **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  $\Delta^9$ -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 %  $\Delta^9$ -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%

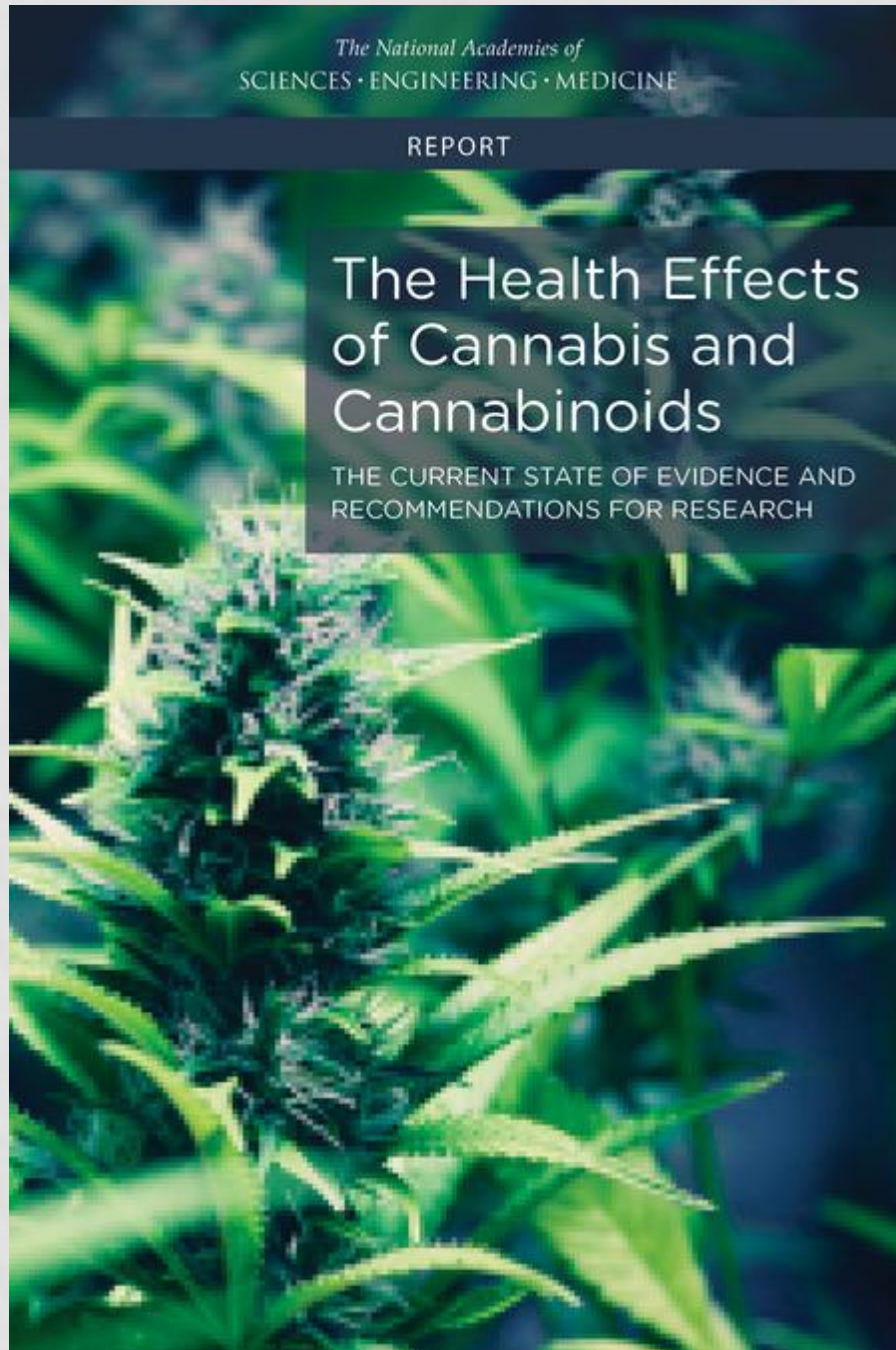


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REPORT

# The Health Effects of Cannabis and Cannabinoids

THE CURRENT STATE OF EVIDENCE AND  
RECOMMENDATIONS FOR RESEARCH



# COMMITTEE OF THE HEALTH EFFECTS OF MARIJUANA

- 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

# PROBLEM CANNABIS USE EVIDENCE

- **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 1<sup>st</sup> 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 TRPV<sub>1</sub>
  - 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.

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