

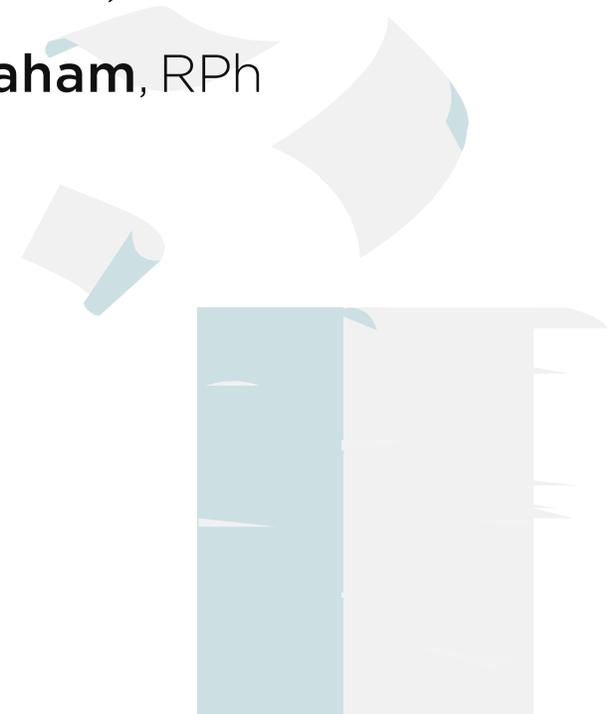
Medical Cannabis

Adverse Effects & Drug Interactions



Presented by

- **Adriane Fugh-Berman, MD**
- **Susan Wood, PhD**
- **Mikhail Kogan, MD**
- **Donald Abrams, MD**
- **Mary Lynn Mathre, RN, MSN, CARN**
- **Andrew Robie, MD**
- **Janani Raveendran, MEd**
- **Kofi Onumah, PharmD, RPh**
- **Rikin S. Mehta, PharmD, JD, LLM**
- **Shauna White, PharmD, RPh**
- **Jawara Kasimu-Graham, RPh**



Important Information

- ▶ The slides will progress at their own pace.
- ▶ Do not attempt to speed up the video.
- ▶ The Post Test will only unlock after the entire video has been viewed.
- ▶ The video can be paused and resumed later.

Learning Objectives

- Identify common adverse effects of medical cannabis use.
- Identify contraindications to medical cannabis use.
- Describe medical cannabis drug interactions.
- Describe respiratory, cardiovascular, immune, neuropsychiatric, reproductive and other risks associated with medical cannabis use.

Introduction to Cannabis

- ▶ ***Cannabis indica*** and ***Cannabis sativa*** are the best-known species.
- ▶ A product's chemical profile is more important than the strain of plant from which it originated.
- ▶ Products should be characterized by analytical chemistry - percentages of cannabinoids and terpenoids.



Compounds in Cannabis

- ▶ Cannabis, like all herbs, is a polypharmaceutical substance.
- ▶ 108 cannabinoids have been isolated (Hanuš 2008).
- ▶ The cannabis-derived cannabinoids of most therapeutic interest are THC and cannabidiol (CBD).
 - Minor cannabinoids include cannabigerol, cannabichromene, and tetrahydrocannabivarin (a short-chain C19 homolog of THC).
- ▶ Terpenoids are common, often aromatic, organic compounds found in many plants. Terpenoids found in cannabis include β -caryophyllene, myrcene, limonene, and pinene.
- ▶ As many as 420 other constituents occur in the plant (Turner et al 1980).

Common Modes of Administration and Formulations

Inhalation by smoking or vaporization

(herbal cannabis, resin, concentrates)

Oral

(prescription cannabinoids, edibles, tinctures)

Oro-mucosal or sublingual

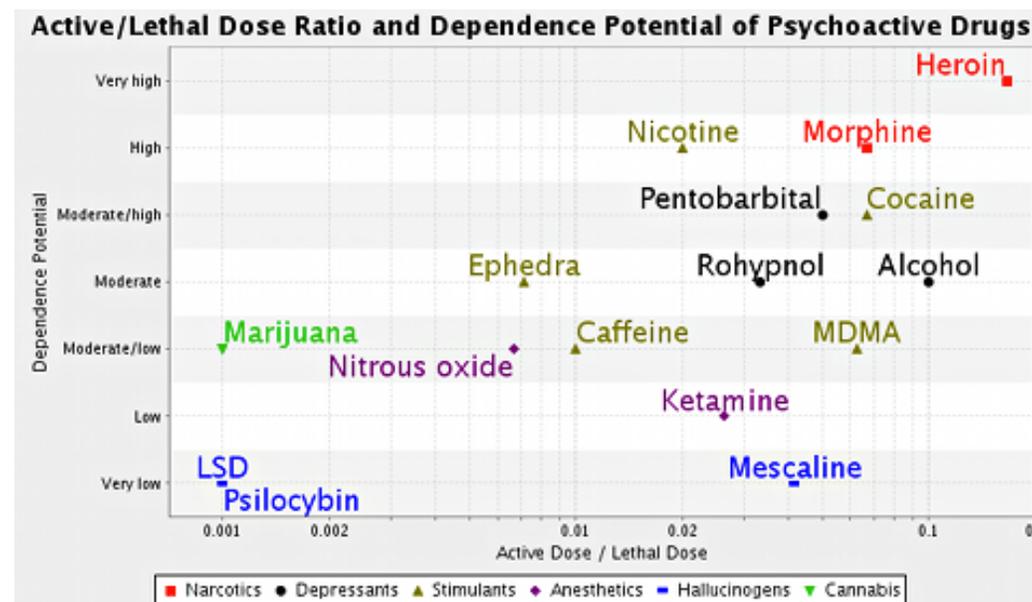
(lollipops, lozenges, nabiximols)

Topical or Rectal

(herbal cannabis, resin, concentrates)

Cannabis Safety Profile

- ▶ Little is known about the safety of individual compounds. Serious adverse effects are rare with cannabis or its constituents.
- ▶ Marijuana has low to moderate dependence potential; the active dose is very far below the lethal dose (Gable et al 2006).



(Adapted from Gable 2006)

Common Adverse Effects

Anxiety

Changes in visual perceptions

Decreased sperm count

Slowed pupillary response to light

Reduced tear flow

Dry mouth

(and possibly associated caries and periodontitis)

Sedation

Altered sense of time

Reduced coordination

Decreased eye blink rate

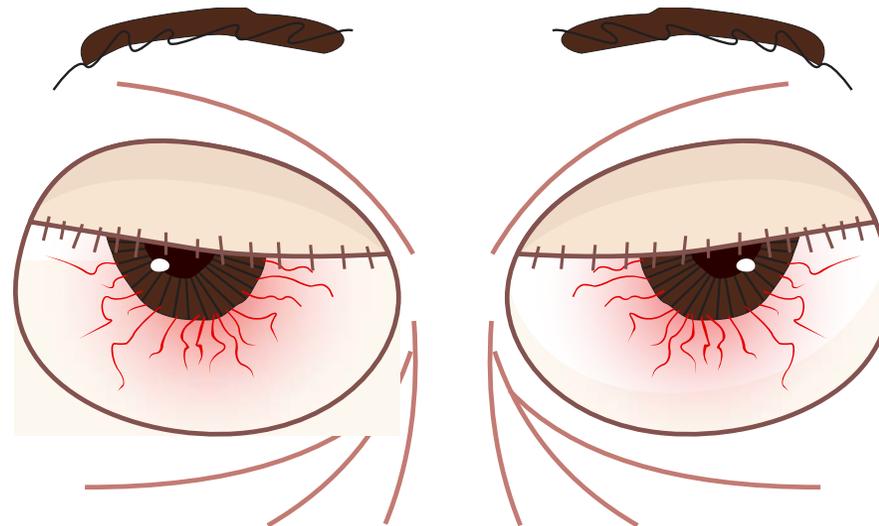
Bronchitis

Ataxia

Dizziness

Cough

Reddened eyes



Dysphoria

(Ashton 1999, Hall and Solowij 1998,
Handbook on Cannabis 2015)

Drug Interactions

Cytochrome P450 Enzymes

- ▶ THC and CBD are metabolized by CYP3A4 and CYP2C9 (Yamaori et al 2012, Watanabe et al 2007).
 - CYP3A4 inhibitors slightly increase THC levels.
 - CYP3A4 inducers slightly decrease THC and CBD levels.
- ▶ CBD, but not THC, is metabolized by CYP2C19 (Stout and Cimino 2014).

Drug Interactions

Cytochrome P450 Enzymes

▶ **THC is a CYP1A2 inducer.**

- Theoretically, THC can decrease serum concentrations of clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine (Flockhart 2007, Watanabe et al 2007).

▶ **CBD is a potent inhibitor of CYP3A4 and CYP2D6.**

- As **CYP3A4** metabolizes about a quarter of all drugs, CBD may increase serum concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil (and other PDE5 inhibitors), antihistamines, haloperidol, antiretrovirals, and some statins (atorvastatin and simvastatin, but not pravastatin or rosuvastatin).
- **CYP2D6** metabolizes many antidepressants, so CBD may increase serum concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids (including codeine and oxycodone).

Drug Interaction Studies

▶ Warfarin

- THC and CBD increase warfarin levels (Yamaori et al 2012).
- Frequent cannabis use has been associated with increased INR.

▶ Alcohol

- Alcohol may increase THC levels (Hartman 2015).

▶ Theophylline

- Smoked cannabis can decrease theophylline levels (Stout and Cimino 2014).

▶ Indinavir or nelfinavir

- Smoked cannabis had no effect (Abrams et al 2003).

▶ Docetaxel or irinotecan

- Cannabis infusion (tea) had no effect (Engels et al 2007).

▶ Clobazam

- In children treated with CBD for epilepsy, CBD increased clobazam levels (Geffrey et al 2015).

Drug Interaction Studies

► CNS depressants

- Cannabis has additive CNS depressant effects with alcohol, barbiturates and benzodiazepines.
- In a small study, cannabis did not have additive CNS effects when combined with opioids (Abrams et al 2011).

Clinical Aspects

Contraindications

➤ **Absolute contraindications**

- Acute psychosis and other unstable psychiatric conditions

➤ **Relative contraindications**

- Severe cardiovascular, immunological, liver, or kidney disease, especially in acute illness
- Cannabis may exacerbate arrhythmia or a history of arrhythmias

(Handbook on Cannabis 2015)

Respiratory Effects

Lung Function



- ▶ A cross-sectional study using National Health and Nutrition Examination Survey (NHANES) data found that up to 20 joint-years* of marijuana use caused no adverse changes in lung function (Kempker et al 2015).



- ▶ The Coronary Artery Risk Development in Young Adults study, a cohort study of 5,115 adults, found no effect of occasional low marijuana use on pulmonary function (Pletcher et al 2012).

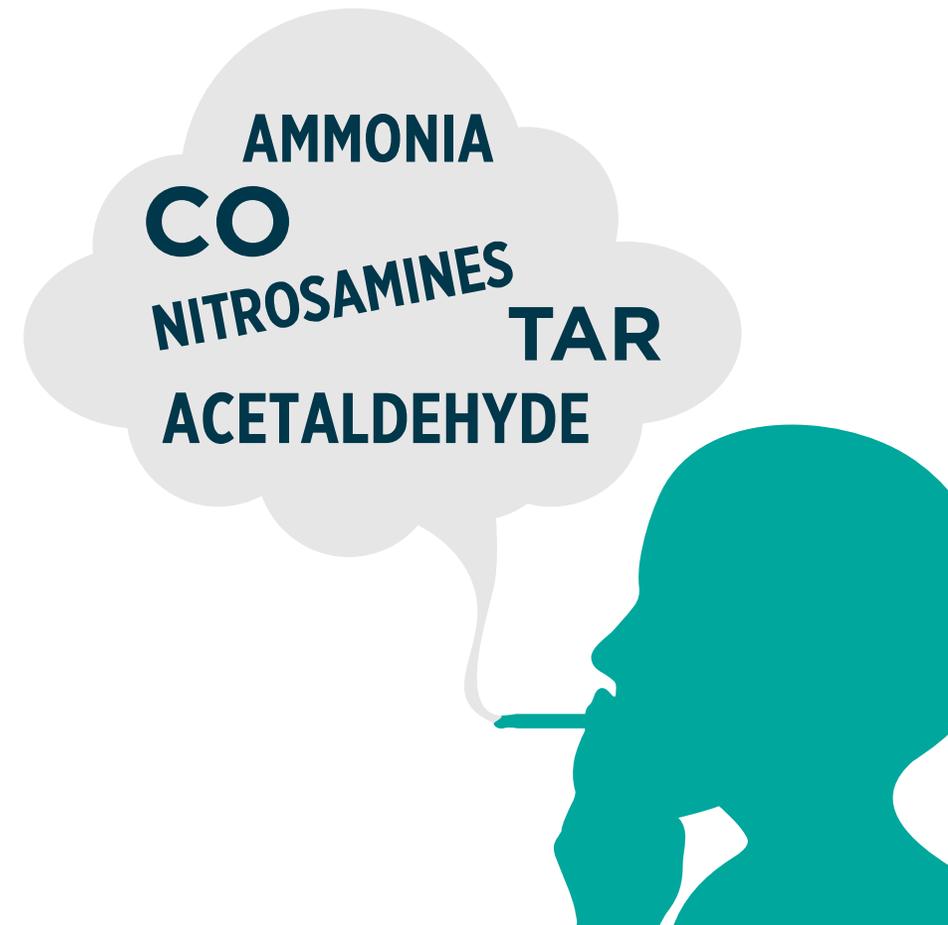


- ▶ In contrast, a cross-sectional Scottish study in 500 adults found evidence of impaired lung function in both cannabis and tobacco smokers (MacLeod et al 2015).

* A joint-year is the equivalent of smoking one joint or pipe bowl of marijuana for one year; it is the number of joints per day multiplied by the number of years of usage. It is a way of standardizing use over time. Ten joint-years could describe one person who smoked a joint a day for 10 year or ten people who smoked a joint a day for one year.

Respiratory Effects Smoked Cannabis

- ▶ Smoked cannabis is clearly associated with symptoms of bronchitis, which resolve after cessation of use (Tashkin 2013, Tashkin 2014).
- ▶ At least 200 compounds occur in cannabis smoke (Sparacino et al 1990): these include carbon monoxide, acetaldehyde, ammonia, nitrosamines, and polycyclic aromatic hydrocarbons (“tars”).
- ▶ Combining tobacco and cannabis appears to have synergistic adverse effects, increasing respiratory symptoms over tobacco use alone (MacLeod et al 2015, Bloom et al 1987).



Respiratory Effects

Vaporization

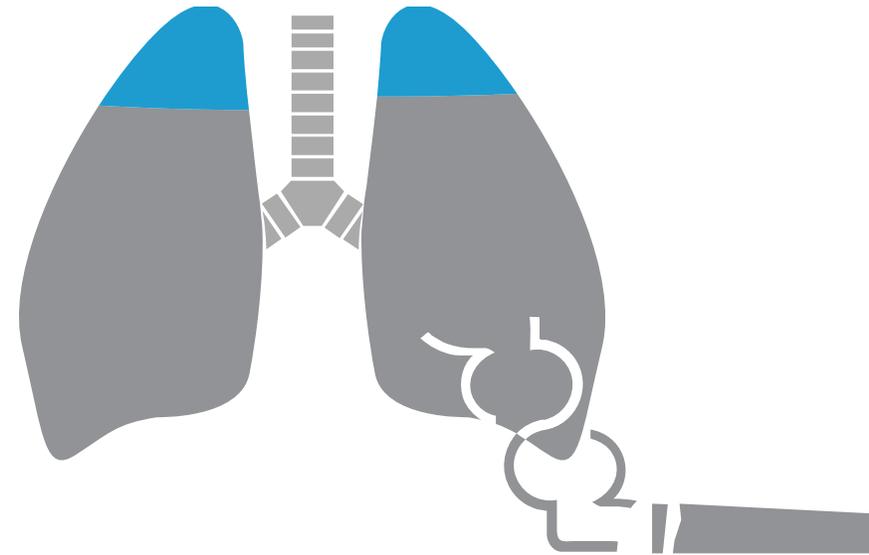
- ▶ A survey of 6,883 cannabis users found that vaporizing, compared with smoking, causes fewer respiratory symptoms (coughing, wheezing, shortness of breath, mucus production) (Earlywine and Barnwell 2007).
- ▶ Analysis of vapor from a vaporizer recovered 89.1% THC and 9.5% smoke toxins; in contrast, cannabis smoke from a pipe recovered 10.8% THC and about 87% smoke toxins (Chemic Laboratories 2003).
- ▶ Vaporization, compared to smoking, generates less carbon monoxide (Abrams et al 2007).



Respiratory Effects

Chronic Obstructive Pulmonary Disease

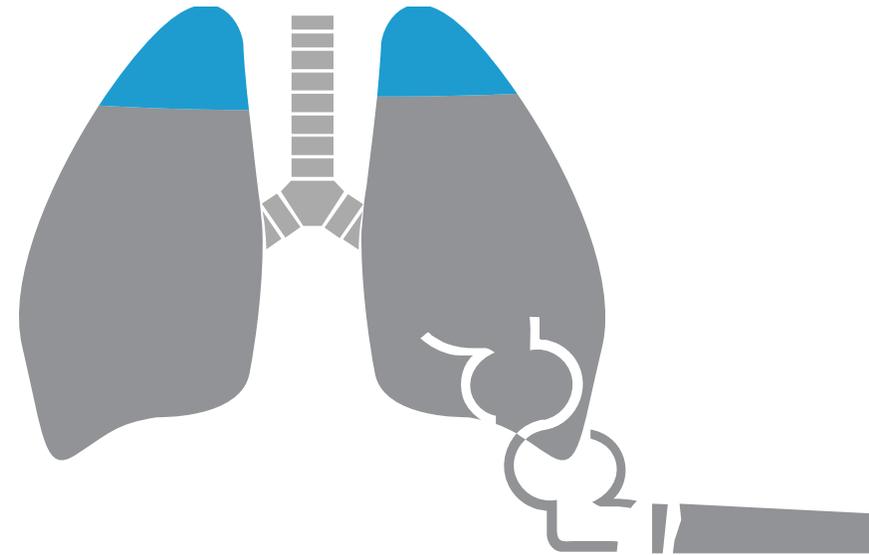
- ▶ Most studies have found that cannabis is not associated with COPD.
- ▶ A survey of 878 adults older than 40 in Vancouver found that cannabis smokers had no more COPD or respiratory symptoms than non-smokers (Tan et al 2009).



Respiratory Effects

Lung Cancer

- ▶ Cannabis does not appear to increase lung cancer risk.
- ▶ A pooled meta-analysis of 6 case-control studies in the US, Canada, UK, and New Zealand that included data on 2,159 lung cancer cases and 2,985 controls found **“little evidence for an increased risk of lung cancer among habitual or long-term cannabis smokers, although the possibility of potential adverse effects for heavy consumption cannot be excluded”** (Zhang et al 2015).



Respiratory Effects

Pneumonia

- ▶ It is unclear whether cannabis is associated with an increased risk of pneumonia.
- ▶ Some case series and studies in immunocompromised patients have noted a link, but no definitive studies have been done.
- ▶ Some effects of smoked cannabis could predispose to pneumonia.
 - Delta-9 tetrahydrocannabinol suppresses alveolar macrophage function and causes replacement of ciliated bronchial epithelium with hyperplastic mucus-secreting bronchial epithelial cells.



Contamination in Cannabis

- ▶ Fungal contamination (*Aspergillus* and *Penicillium* species) in marijuana samples has been demonstrated. Contamination with fungal or bacterial pathogens could increase risk of pneumonia and other respiratory problems (McPartland and Pruitt 1997, McLaren et al 2008).
 - Lack of ventilation and high humidity increase the likelihood of mold growth in indoor growing operations (Martynty et al 2013).
- ▶ While medical cannabis may be safer than unregulated cannabis, testing for fungal or bacterial contamination varies by jurisdiction.
- ▶ There are concerns that pesticides may pose risks in cannabis products (McLaren et al 2008).

Cardiovascular Effects

- ▶ THC can cause tachycardia; chronic users may develop bradycardia.
- ▶ Cannabis can cause changes in blood pressure.
 - High doses can cause orthostatic hypotension and syncope (Handbook on Cannabis 2015).
 - Cannabis can cause an acute increase in blood pressure (Frost et al 2013).
- ▶ Cannabis can increase the risk of angina (Frost et al 2013).
- ▶ Rarely marijuana can trigger an acute myocardial infarction (Mittleman et al 2001).
- ▶ In patients who have had a myocardial infarction, an 18-year follow up study showed no conclusive evidence that smoking marijuana increased mortality (Frost et al 2013).
- ▶ Case reports have associated cannabis use with acute coronary syndrome, arrhythmias, sudden cardiac death, cardiomyopathy, transient ischemic attack, stroke (Thomas et al 2014, Jouanjus 2014).

Immunologic Effects

Lymphocytes

- ▶ Cannabis does not appear to affect immune cells.
- ▶ A 21 day RCT of 62 people with HIV that compared placebo to smoked cannabis and dronabinol 2.5 mg found no significant pattern of effects on T cell subpopulations, B cells, NK cells and other measures of immune function (Bredt 2002, Abrams et al 2003).
- ▶ A decade-long longitudinal study of 481 HIV-infected men found no association between cannabis use and CD4/CD8 decline (Chao et al 2008).



Immunologic Effects

Allergies and Hypersensitivity

- ▶ Cannabis pollen inhalation has been associated with allergic rhinitis, conjunctivitis, and asthma.
- ▶ One case of erythema multiforme-like recurrent drug eruption thought to be associated with cannabis use was reported.
- ▶ Skin exposure to plant material has been associated with urticaria, generalized pruritus, and periorbital angioedema.
- ▶ Anaphylaxis has been reported after intravenous use of cannabis and ingestion of hemp seed-encrusted seafood (patient tolerated a subsequent oral seafood challenge).
- ▶ Industrial hemp dust exposure has been implicated in byssinosis, an occupational obstructive lung disease associated with organic textile dust exposure.
- ▶ A case of allergic bronchopulmonary aspergillosis attributed to fungal contamination has been described.

(O'Campo 2015)

Neuropsychiatric Effects

Cognitive Function

- ▶ Long-term cannabis users exhibit deficits in prospective memory and executive function (Montgomery 2012).
- ▶ In depressed and non-depressed regular marijuana users, there was an inverse association between marijuana use and verbal learning function.
 - The effect was not moderated by depression (Roebke 2014).

Adolescent marijuana users demonstrated significantly smaller medial orbitofrontal and inferior parietal volumes (regions of the brain associated with higher order cognition); smaller medial orbitofrontal volumes were associated with poorer complex attention.

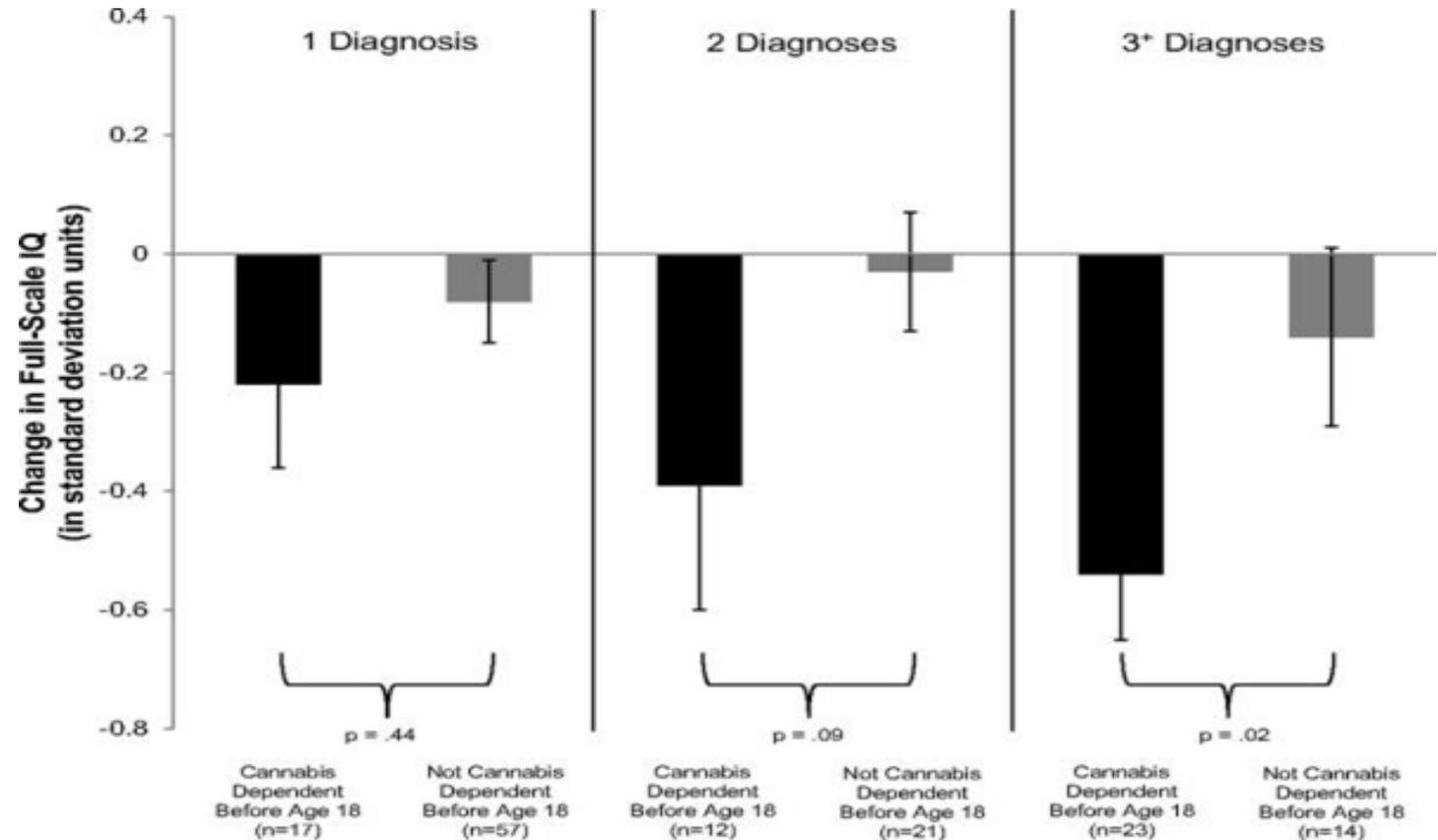
(Price et al 2015)



Neuropsychiatric Effects

Cognitive Function

- ▶ A study looked at the impact of cannabis use during adolescence on subsequent cognitive function.
- ▶ Use of cannabis before age 18 lowered IQ 20 years later.



(Meier et al 2012)

Neuropsychiatric Effects

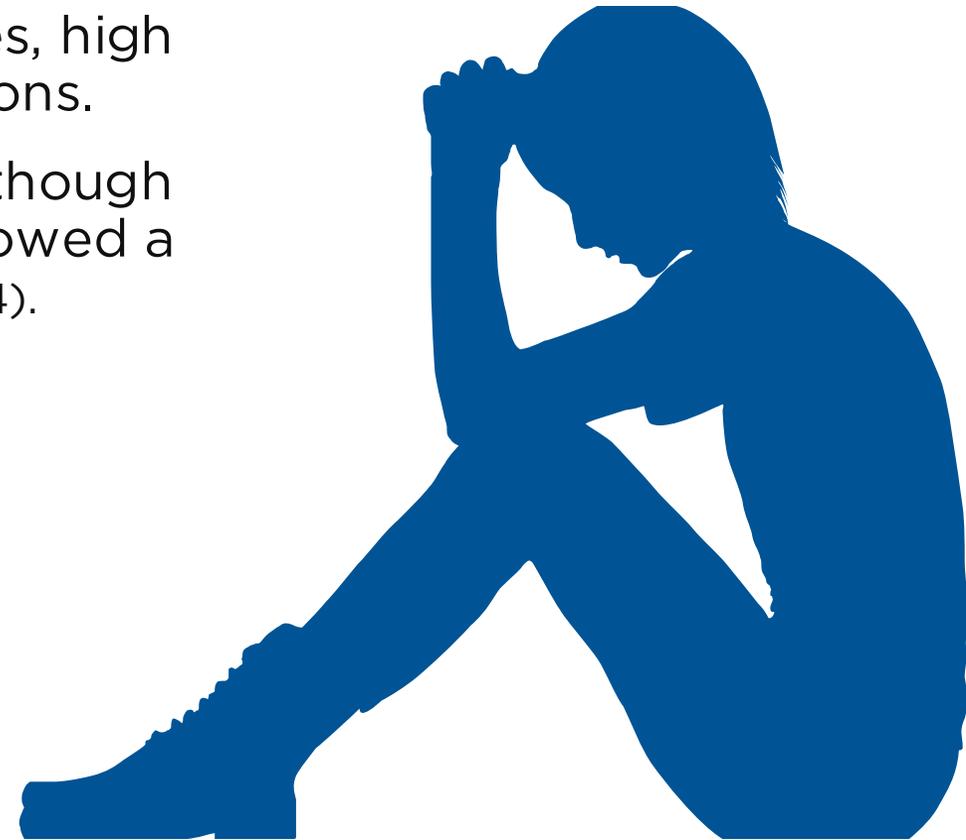
Adolescence

- ▶ Cannabis use in adolescence may increase psychotic symptoms later in life.
- ▶ A systematic review of the impacts of cannabis use during adolescence on various psychosis symptoms later in life was conducted.
- ▶ Authors concluded that “there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life” (Moore et al 2007).
- ▶ Animal studies also show that cannabis use during adolescence, but not adulthood, increases later psychiatric problems (Rubino et al 2012).

Psychiatric Effects

Anxiety and Depression

- ▶ Although cannabis acts as an anxiolytic in low doses, high doses can be anxiogenic and can elicit panic reactions.
- ▶ Chronic use may increase the risk of depression, although studies are mixed. A meta-analysis of 14 studies showed a weak risk (HR 1.17, 95% CI 1.05-1.30) (Lev-Ran et al 2014).



Psychiatric Effects

Psychosis/Schizophrenia

- ▶ Whether or not cannabis can cause psychosis is debated.
- ▶ Studies suggest that people at risk for schizophrenia run a higher risk of psychosis outcomes after cannabis use (Morrison et al 2015).
- ▶ A study of cannabis use in 1237 people with schizophrenia, who had ever used cannabis, found no additive effect of cannabis use on cognitive dysfunction (Power 2015).
- ▶ Smoking cannabis with a significant proportion of CBD may produce fewer psychotic symptoms (Morgan and Curran 2008, Schubart et al 2011).
- ▶ It has been suggested that cannabis has antipsychotic effects, but a Cochrane systematic review of cannabis and schizophrenia noted that studies were limited, and that “currently evidence is insufficient to show cannabidiol has an antipsychotic effect” (McLoughlin 2014).

Psychiatric Effects

Dependence

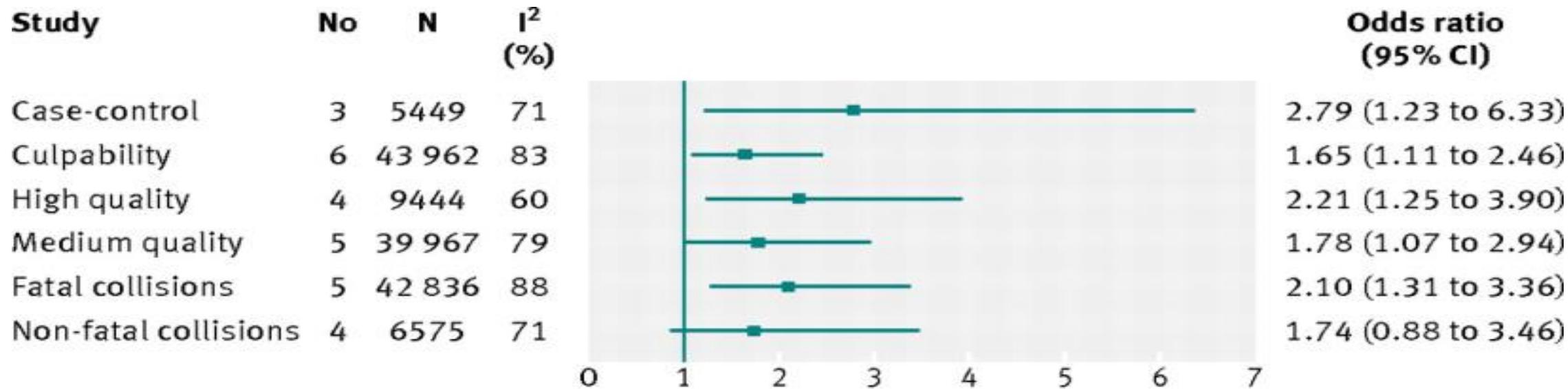
- ▶ Cannabis dependence may occur: the estimated global prevalence is 0.23% in males and 0.14% in females (Degenhardt et al 2013).
- ▶ Prevalence peaks in the 20-24 years age group, and decreases steadily with age.
- ▶ In a survey of 6,917 marijuana users, 15% met the criteria for a marijuana use disorder. People who met the criteria for marijuana use disorder also were correlated with weekly marijuana use, early marijuana use, other substance use disorders, substance abuse treatment, and serious psychological distress (Wu et al 2012).
- ▶ Marijuana usage goes up in states that pass medical marijuana laws. However, the dependence rate among marijuana users does not differ between states with or without medical marijuana laws (Cerdeira et al 2012).

Driving Under the Influence

- ▶ THC alters perception and psychomotor performance, which may contribute to an increased risk of causing a traffic accident.
- ▶ A systematic review and meta-analysis of nine observational studies found that acute cannabis consumption is associated with an increased risk of motor vehicle crashes, especially for fatal collisions (Asbridge et al 2012).
- ▶ A case-control study associated THC with a 29% increase in unsafe driving, compared to 101% for alcohol (Bédard et al 2007).



Driving Under the Influence



Pooled odds ratio (95% CI) of motor vehicle collision risk with tetrahydrocannabinol for subgroups of studies.

Reproductive Effects

Exposure During Pregnancy

Cannabis use during pregnancy is not recommended.

- ▶ Heavy use of cannabis during pregnancy may cause adverse effects on early neurodevelopment, including subtle cognitive impairment and decrements in executive functioning later in life.
- ▶ Cannabis use has not been shown to increase the risk of congenital anomalies.
- ▶ Some but not all studies have shown a decrease in fetal growth.
- ▶ There is a possible increased risk of preterm birth.

(Fried et al 2003, Goldschmidt et al 2012)



Reproductive Effects

Lactation and Fertility

Cannabis use during lactation is not recommended.

- ▶ THC and its metabolites are excreted in breast milk.
- ▶ Infants exposed to marijuana during lactation had lower scores on the Psychomotor Developmental Index compared to non-exposed infants (effects could not be separated from prenatal exposure).

Fertility effects in men

- ▶ Some studies indicate that chronic use of marijuana may decrease plasma testosterone and decreases sperm count, concentration, and motility.

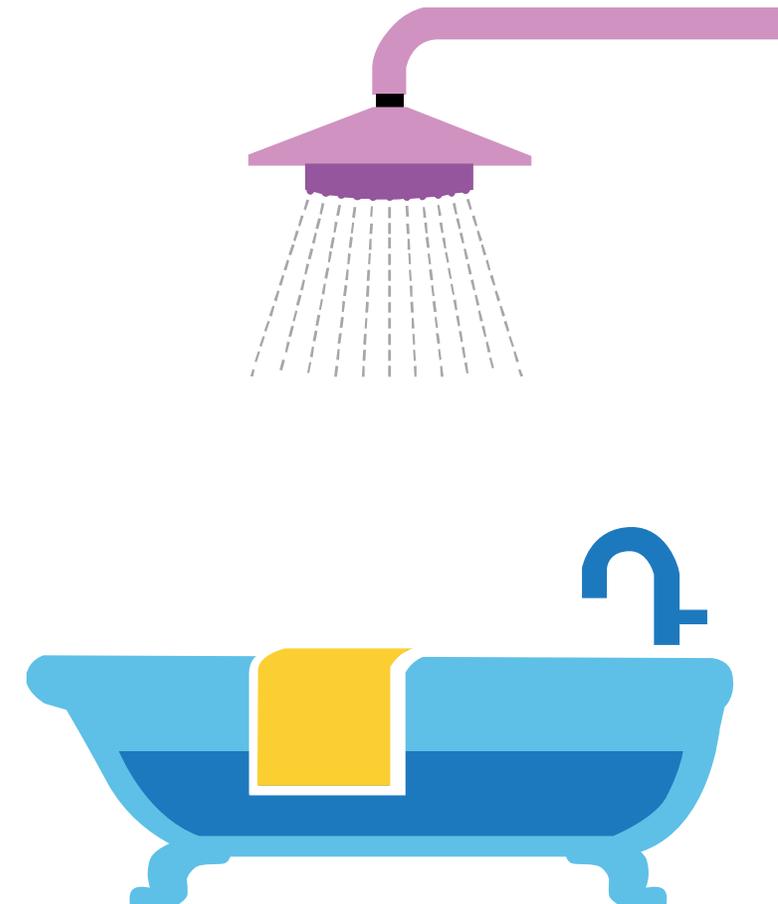
(Reprotox.org, Metz and Stickrath 2015)



Cannabinoid Hyperemesis Syndrome

- ▶ Chronic cannabis use may be associated with Cannabinoid Hyperemesis Syndrome (also called Cyclic Vomiting Syndrome).
- ▶ It is characterized by episodes of nausea and vomiting, abdominal pain, and sometimes polydipsia.
- ▶ Obsessive hot-water bathing may be observed, as it alleviates symptoms.
- ▶ The syndrome can lead to weight loss or acute renal failure from dehydration.
- ▶ The etiology of CHS is thought to be activation of CB₁ receptors that can reduce gastric emptying.

(Galli et al 2011, Woods et al 2014, Beech et al 2015, Iacopetti and Packer 2014, Yap and Luther 2012, Habboushe and Sedor 2014)



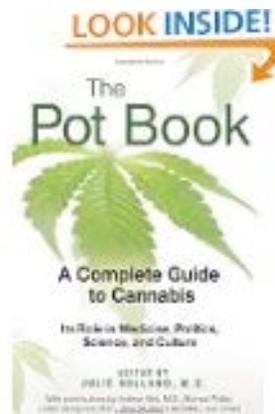
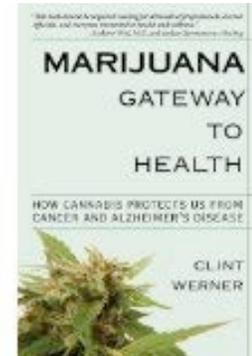
Summary

- ▶ Cannabis is generally well-tolerated, and serious adverse effects, including increased risk of cardiovascular events, are rare.
- ▶ Adverse changes in cognitive function, especially executive function, may occur, especially with fetal or adolescent exposure.
- ▶ Cannabis should be avoided by adolescents, pregnant women, and nursing mothers.
- ▶ Cannabis should be avoided in those at risk of psychosis.
- ▶ Many studies show driving impairment, but on a much lower scale than alcohol.
- ▶ Drug interactions are a concern.
 - Cannabis enhances CNS depressant effects when combined with alcohol, barbiturates and benzodiazepines, but probably not opioids
 - THC induces CYP1A2, and can reduce levels of drugs metabolized by CYP1A2.
 - CBD inhibits CYP3A4 and CYP2D6, and can increase levels of drugs metabolized by these isoenzymes. CYP3A4 metabolizes about a quarter of all drugs.

Resources



- **DCRx** - doh.dc.gov/dcrx
- **International Cannabinoid Research Society (ICRS)** - <http://www.icrs.co/index.html>
- **International Association for Cannabinoid Medicines (IACM)** - <http://www.cannabis-med.org>
- **Patients Out of Time** - <http://www.medicalcannabis.com>
- **University of California's Center for Medicinal Cannabis Research** - <http://www.cmcr.ucsd.edu>
- **The Canadian Consortium for the Investigation of Cannabinoids** - <http://www.ccic.net>



Resources

For more information on prescribing in the District and to become a recommending physician visit:



doh.dc.gov/mmp

Please visit DCRx for a full list of references and more information on these and other treatment-related subjects.



doh.dc.gov/dcrx

Questions can be sent by email to doh.mmp@dc.gov or by regular mail to:

Medical Marijuana Program
Health Regulation and Licensing Administration
899 N. Capitol Street, NE
2nd Floor
Washington, DC 20002