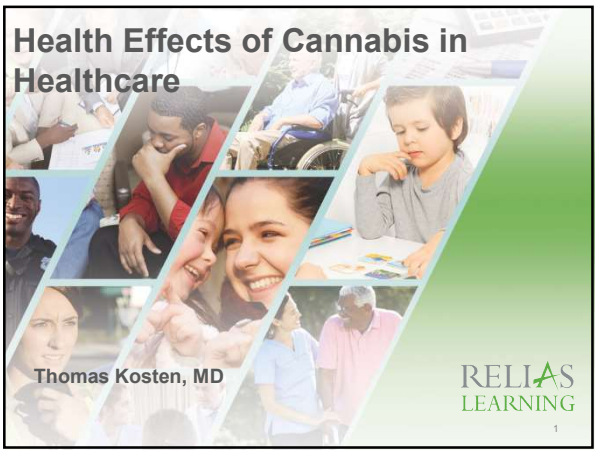
Health Effects of Cannabis in Healthcare



Thomas Kosten, MD

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Speaker

Dr. Kosten is Waggoner Chair & Professor of Psychiatry, Pharmacology, Immunology and Neuroscience & Director of the Institute for Clinical and Translational Research at Baylor. He is the founding Vice Chair for Addiction Psychiatry of the ABPN, Past President of both the American Academy of Addiction Psychiatry and College on Problems of Drug Dependence, and Distinguished Life Fellow in the American Psychiatric Association.

Objectives

- Describe the health effects of cannabis and cannabinoid use.
- Explain how to provide cannabis treatment for chemotherapy induced nausea and vomiting, chronic pain and multiple sclerosis related spasticity.
- Explain how to provide care for people with mental health complications due to cannabis and cannabinoid abuse.

Marijuana Bud:
The Star of this Presentation

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Cannabis in Healthcare - Overview

- This is a pivotal time in the world of cannabis policy and research for healthcare. Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate.
- This presentation provides a broad set of evidence-based research conclusions on the health effects of cannabis and cannabinoids. While the health effects of cannabis are clear on some health endpoints such a vomiting, pain and spasticity, many endpoints are understudied, such as epilepsy in pediatric populations; symptoms of posttraumatic stress disorder; childhood and adult cancers; cannabis-related overdoses and poisonings. .

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Cannabis in Healthcare – Topics

1. Changing Epidemiology & Pharmacology:
   - Past 40 years
   - Neurobiology
   - Native & synthetic cannabinoids
2. Therapeutic effects: pain, vomiting, multiple sclerosis
3. Cancer incidence
4. Respiratory & Cardio-metabolic risks & Immune function
5. Pregnancy, postnatal & childhood outcomes
6. Injury and death
7. Mental health
   - Psychosocial outcomes
   - Problem cannabis use

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Section 1
Changing Epidemiology & Pharmacology:
- Past 40 years
- Neurobiology
- Native & synthetic cannabinoids

Section 1a
Cannabinoid Epidemiology

Marijuana Epidemiology and Pharmacology

- Marijuana (MJ) use has significantly increased among high-school students from 1995 to 2015 and markedly fluctuated since 1975
- Use inversely related to perception of harm from MJ and to state decriminalization
- Street THC (tetra hydrocannabidiol) potency has increased substantially in past 2 decades – from .05% THC to 5.0% and as high as 15%
- "Kush" uses "synthetic THC" that are full agonists rather than the partial agonist of natural THC

Epidemiology

- Marijuana is the most widely used illicit drug both in the U.S. & world-wide
- More than 75 million (over 34%) of Americans 12 years or older have tried it at least once & almost 19 million have used it in the past year. Prevalence of use in adults is approximately 4%
- Average age of 1st use has been declining:
  - 12-17 year olds – 13.6 years
  - 18-25 year olds – 16 years
- While most discontinue marijuana by their mid-20's, a subset maintain daily, long-term use

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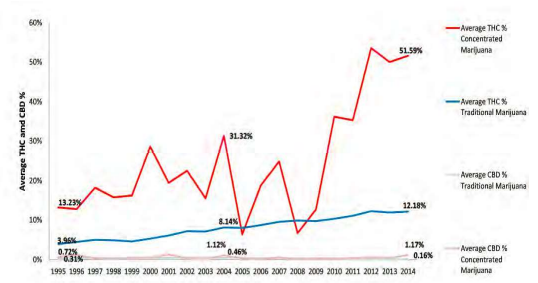
Marijuana potency: Dramatic rise from 2008



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States Legalize Medical Cannabis

1996 - California
1998 - Alaska, Washington, Oregon
1999 - Maine
2000 - Hawaii, Nevada, Colorado
2004 - Montana, Vermont
2006 - Rhode Island
2007 - New Mexico
2008 - Michigan
2010 - Arizona, New Jersey
2011 - Delaware
2012 - Massachusetts, Connecticut
2013 - Minnesota, New Hampshire
2014 - Illinois, New York, Maryland
2016 - Ohio, Pennsylvania
2017 - Louisiana*

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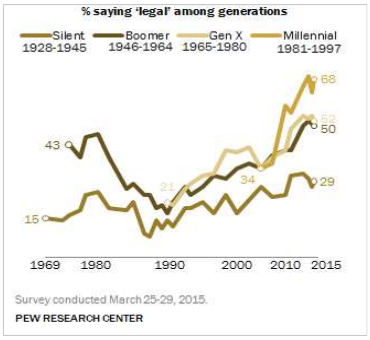
Generational Differences favoring Legalizing MJ



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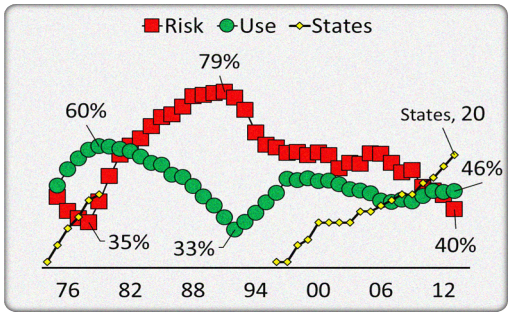
MJ Use and Fear of Risks move Inversely



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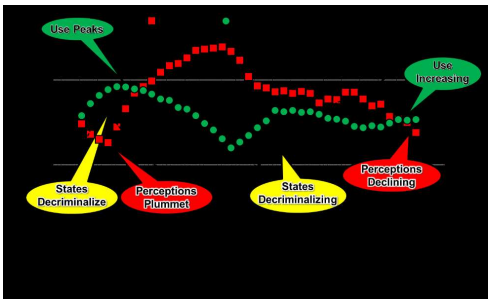
MJ Use (green) vs. Harm perception (red): 1975-2015



Section 1b
Cannabinoid Neurobiology

Cannabinoid Neurobiology
(continued)

- THC receptors:
  - CB-1 in brain;
  - CB-2 in periphery, not psychoactive, immune function
- Natural ligand: Anandamide – fatty acid
- Most CB-1 receptors in cortex (basic cognitive functioning), hippocampus (memory functions), & cerebellum (motor coordination)
- Retrograde signaling to reduce neuronal stimulation
- Anandamide, which is degraded by brain enzymes within minutes, is quite different from THC and synthetic cannabinoids, which have much longer half-life of approximately 7 days

Endogenous Cannabinoid Neurobiology

- Anandamide is a fatty acid that is the natural ligand for the CB1 cannabinoid receptor
- Anandamide is degraded by brain enzymes in minutes
- Two main degrading enzymes are COX2 and FAAH
- FAAH – Fatty acid amide hydrolase can be inhibited by new medications to markedly prolong the duration of anandamide activity and CB1 receptor stimulation
- These FAAH inhibitor medications are being developed as analgesics without the tolerance, dependence and abuse potential of opiates like morphine

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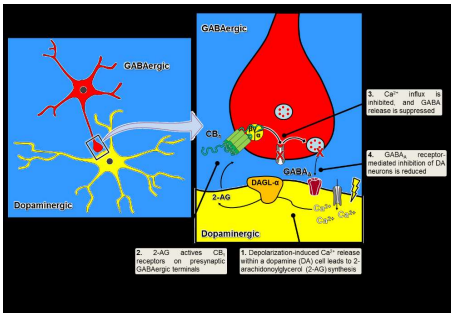
Molecular Actions of Cannabinoids:
Dopamine and GABA neurons



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Physiologic Effects of THC

- Respiratory effects – acutely, dilatation of bronchial tubes; chronically, decreased bronchial diameter, & worsening of breathing problems. Chronic cough and bronchitis
- Leads to similar respiratory problems as tobacco smoking – 1 marijuana cigarette deposits about as much tar as 4 of tobacco
- Cardiac – increased heart rate & increased cardiac work load
- Urinary – increased urinary frequency
- G-I – decreased nausea/vomiting

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Psychological Effects

- Mood changes are a function of dose, “set,” & “setting” as well as route of administration
- Common changes:
  - Altered consciousness, mild euphoria, relaxation
  - Giddiness, increased then decreased social interaction
  - Sexual arousal, slowing of time, increased hunger (“munchies”)
  - Impaired short term memory & distance perception, sleepiness

Mechanism of Marijuana Withdrawal

- Withdrawal from marijuana is associated with release of corticotropin releasing factor (CRF) in the amygdala
- Similar increase in CRF is found during withdrawal from opiates, cocaine, & alcohol
- CRF may be responsible for the stress-like symptoms noted during withdrawal – nervousness, anxiety, restlessness, & sleep disturbances
- This suggests that long-term marijuana use alters CRF function in the limbic system similar to other drugs of abuse

de Fonseca et al., 1997

Section 1c
Synthetic Cannabinoids

Cannabinoid Pharmacology

- Is fat soluble & readily absorbed in tissues with high fat content, e.g., brain, testes
- Effects of 100 to 300 fold higher potency THC – more rapid intoxication & with smaller amount
- Effects of high potency, full agonist “synthetic THC” – more psychotic and medical comorbidity with intoxication and toxicity from “weed” used as substitute substance for these MJ look-a-likes (over 60 cases reported in last few years of new onset psychosis with no previous mental illness)

Marijuana Bud:
New high potency breeds are a Threat

Synthetic Cannabinoids: Much Bigger Threat

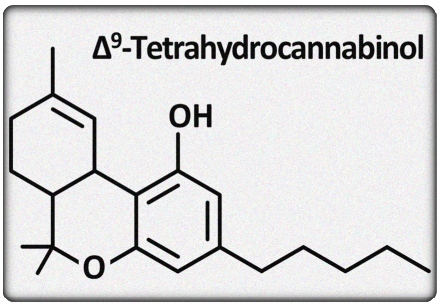
Synthetic cannabinoid Threat

- Synthetic cannabinoid products are herbs
- Sprayed with chemical additives to mimic the psychoactive effects of botanical marijuana,
- BUT are significantly more dangerous to the user.

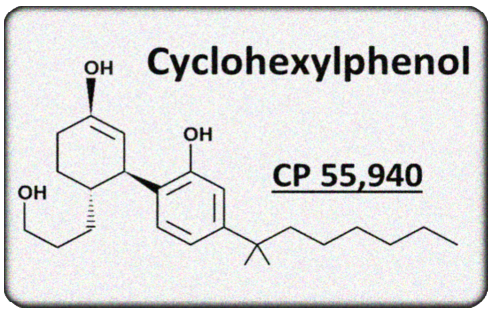
- Bright colored packaging resembles candy for kids
- Use cannot be easily detected in urine or blood samples.

- Packages are marked “not for human consumption,”
- BUT are marketed as legal and safe
- Viewed as “safe alternative” to marijuana.

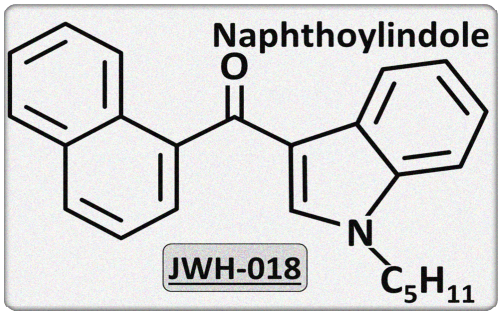
Marijuana – THC – Partial agonist



Synthetic Cannabinoids – Full Agonist



Synthetic Cannabinoid – Agonist (400 others)

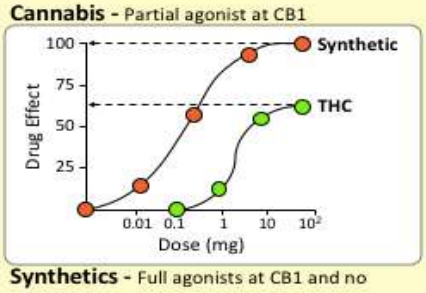


Synthetics: Keeping up with Growing Supply

# Unique compounds	# DEA seizures
• Over 400 available	• Compare to: MJ
• Year - # unique	• Year - # seizures
• 2010 - 18	• 2010 – 3285 :22000
• 2011 – 32	• 2011 – 23000 :19000
• 2012 - 46	• 2012 - 43000 :17000
• 2013 - 47	• 2013 – 33000 :17000
	• 2014 - 40000 :15000

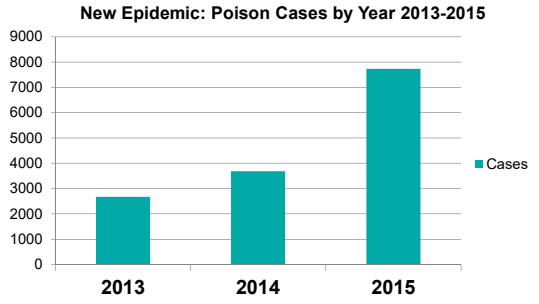
Synthetic Cannabinoids – Much More Potent

Cannabis - Partial agonist at CB1



Synthetics - Full agonists at CB1 and no cannabidiol

Synthetics Toxicity : US Poison Control reports



Similar & additional Effects

Cannabis versus Synthetics

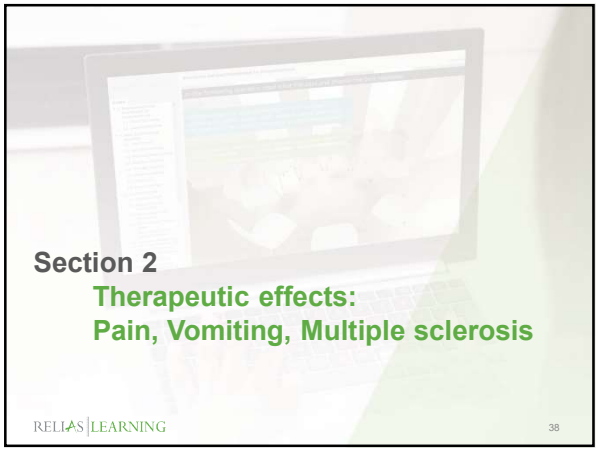
Similar Effects	Additional Effects
Elevated mood	Agitation
Altered perception	Violent behavior
Drowsiness	Suicidal thoughts
Impaired coordination	Increased blood pressure
Reddened eyes	Seizures
Increased appetite	Muscle spasms
Nausea/vomiting	Low potassium
Increased heart rate	Kidney damage
Increased/reduced anxiety	Coma
Memory deficits	Death
Acute psychosis	

Case of Synthetic Cannabinoid (SC) Toxicity (1)

- **Initial Presentation**
  - **18yo M with no PMH brought in by EMS for altered mental status and lethargy after SC use**
  - Loss of consciousness observed at home
  - On arrival to Emergency Department, vomitus on shirt, has a generalized tonic-clonic seizure
  - Vitals: T 104°F, BP 99/39, HR 140 bpm
- **Complications**
  - Developed respiratory failure overnight requiring intubation and admission to Intensive Care Unit
  - Chest X-ray suggestive of aspiration pneumonia; started on IV antibiotics

Case of Synthetic Cannabinoid (SC) Toxicity (2)

- **Treatment Outcome**
  - Mental and respiratory status gradually improved with treatment/supportive measures for 2 days in ICU
  - Transferred back to floor and transitioned to PO antibiotics
  - After continued monitoring and 4 total days of hospitalization, patient was discharged with antibiotics and Primary Care follow-up
  - **The patient was counseled on the harms of SC usage but insisted that the current hospitalization was "just one bad high" and planned to resume using SCs after discharge**



Section 2
Therapeutic effects: Pain, Vomiting, Multiple sclerosis

Therapeutic Effects (statistically significant)

- Adults with chronic pain experience a clinically significant reduction in pain symptoms with cannabinoids
- Chemotherapy induced nausea and vomiting responds to THC or dronabinol 10 mg Q4h as an effective anti-emetic
- Adults with multiple sclerosis (MS) related spasticity show relief by oral cannabinoids
- Appetite stimulation helps cachexia
- Glaucoma: smoking cannabis significantly lowers intraocular pressure, but not nerve damage (better agents)
- For all these conditions, the effects of cannabinoids are modest

Commercial / Legal Formulations (1)

- Research cannabis = vaporized/smoked flower form from NIH with relatively low THC levels

- FDA tested commercial products
- Δ-9-tetrahydrocannabinol (THC) —dronabinol and nabilone; developed in 1985: Phase 3 FDA testing (still)
- Nabiximols, an oromucosal spray of cannabis plant extract with a 1:1 ratio of THC to cannabidiol: Phase 3

Commercial / Legal Formulations (2)

- State sold cannabis products (transdermal for pain) differ markedly from research cannabis or FDA products
- The efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States is UNKNOWN

- Legal access to low THC / high-cannabidiol products for **other "legal uses"**: posttraumatic stress disorder, cancer, epilepsy, cachexia, glaucoma, HIV/AIDS, traumatic brain injury, Tourette syndrome, addiction, anxiety, depression, sleep disorders, degenerative neurological conditions [Alzheimer's, amyotrophic lateral sclerosis, Huntington's, Parkinson's, vascular dementia]

Cannabis Efficacy for Pain

- 3 key reviews of chronic pain efficacy:
- Snedecor et al. 2013: only pain from spinal cord injury and tested only dronabinol.
- Andreae et al., 2015: only peripheral neuropathy and tested only cannabis in flower form via inhalation

- Whiting et al. 2015: comprehensive medical conditions tested in 28 randomized trials (2,454 participants).
- Drug- # trials: nabiximols-13; smoked plant flower- 5; THC oral spray- 3; oral THC- 1; nabilone- 5.
- Efficacy: 40% greater efficacy than placebo (OR=1.4; CI = 1.0-2.0); Bayesian OR=3.2; CI = 1.6-7.2

Cannabis Efficacy for Vomiting

- Oral nabilone and dronabinol were FDA approved for chemotherapy-induced nausea & vomiting 30 years ago
- 28 trials (1,772 pats) testing nabilone (14), THC (6), levonantradol (4), dronabinol (3) and nabiximols (1).
- Efficacy: OR 3.82, 95% CI = 1.55–9.42 (vs placebo)
- Patient preference for cannabinoid: RR 3.2, CI = 2.2–4.7
- More cannabinoid adverse events: dizziness, dysphoria, euphoria, "feeling high," and sedation
- Dronabinol is equivalent to ondansetron, but not tested against neurokinin-1 inhibitors (more widely used)
- Effectiveness of cannabidiol or cannabidiol-enriched cannabis needs testing to avoid THC psychoactive effects

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Cannabis Efficacy for Spasticity

- 11 studies with MS and 3 with spinal cord paraplegia
- Drugs tested: nabiximols and nabilone
- Efficacy: −0.76 (CI = −1.38 to −0.14) on a 0 to 10 self-report scale
- Cannabinoids "probably ineffective" for reducing objective measures of spasticity in the short term (6–15 weeks), but "possibly effective" for objective measures at 1 year

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Analgesia through cannabinoid mechanisms

- Both irreversible (e.g., URB-597) and reversible (e.g., OL-135) inhibitors of FAAH increase brain anandamide levels, increased sensitivity to the pharmacologic effects of injected anandamide, and a CB_1-mediated decrease in pain sensitivity in the tail immersion, hot plate, and formalin tests. Thus, FAAH inhibitors such as URB-597, as well as MAGL inhibitors, produce anti-nociception.
- CB_2 receptor is a critical component of inflammatory pain
- CB_1 cannabinoid and opioid receptors have similar anatomical distributions in the dorsal horn of the spinal cord and in several brain structures

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Therapeutic cannabinoid mechanisms: Pain, Sleep, Anticonvulsant

- Low dose THC prevents tolerance to morphine developing
- Cannabinoids ameliorate pain and improve quality of sleep as well as spasticity in MS patients
- 90% of MS patients report improvement with cannabis.

- Cannabidiol has an anticonvulsant effect in children refractory to other therapies
- First noted in 1940s, children poorly controlled on conventional anticonvulsants improve with cannabis

- NO controlled clinical trials as anticonvulsant

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Therapeutic cannabinoid mechanisms: Eating

- THC increases Appetite by enhancing desire or "craving" for food via limbic system & hypothalamus stimulation

- THC increases weight by raising levels of leptin, ghrelin, and the melano-cortins
- Endocannabinoids increase adipocytes' leptin production;
- Ghrelin is released during food deprivation & signals the hypothalamus of the need for energy intake. Ghrelin then up-regulates hypothalamic endocannabinoid levels

- Controlled trials failed for cancer cachexia & anorexia

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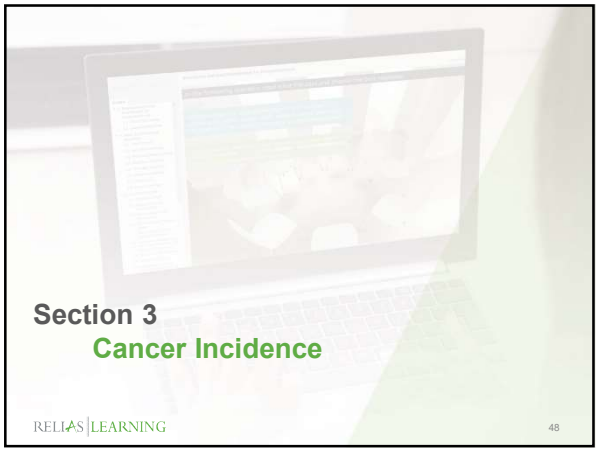

Section 3
Cancer Incidence

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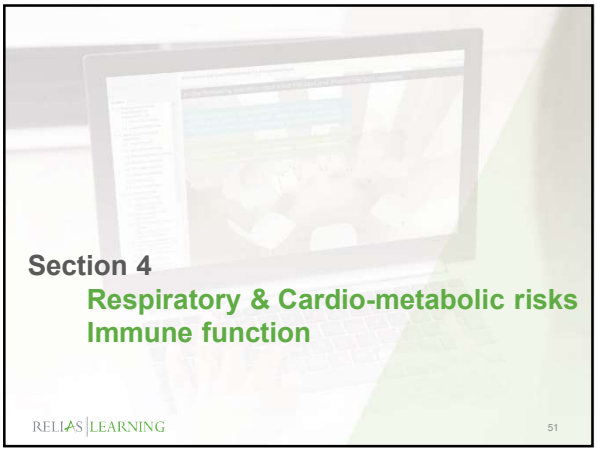
Cancer

- There is moderate evidence of no association between cannabis smoking and the incidence of lung cancer.
- There is moderate evidence of no association between cannabis use and the incidence of head and neck cancers.
- There is limited evidence of a statistical association between current, frequent, or chronic cannabis smoking and **non-seminoma-type testicular germ cell tumors**.

Cancer (continued)

- There is no association between cannabis smoking and the incidence of esophageal cancer.
- There is no association between cannabis use and the incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer.
- There is no association between parental cannabis use and a subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring.



Section 4
Respiratory & Cardio-metabolic risks
Immune function

Respiratory Disease

- There is substantial evidence for an association between long-term cannabis smoking and worse respiratory symptoms and more frequent chronic bronchitis episodes
- There is moderate evidence of an statistical association between cannabis smoking and improved airway dynamics with acute use, but not with chronic use
- There is moderate evidence of an association between cannabis smoking and higher forced vital capacity (FCV)
- There is moderate evidence of an association between cessation of cannabis smoking and improved respiratory symptoms

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Respiratory Disease (continued)

- There is limited evidence of an association between occasional cannabis smoking and an increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use.
- There is no evidence for an association between cannabis smoking and hospital admissions for COPD.
- There is no evidence for an association between cannabis smoking and asthma or its exacerbation.

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Cardio-metablic Risk

- Unclear whether and how cannabis use is associated with heart attack, stroke, and diabetes.

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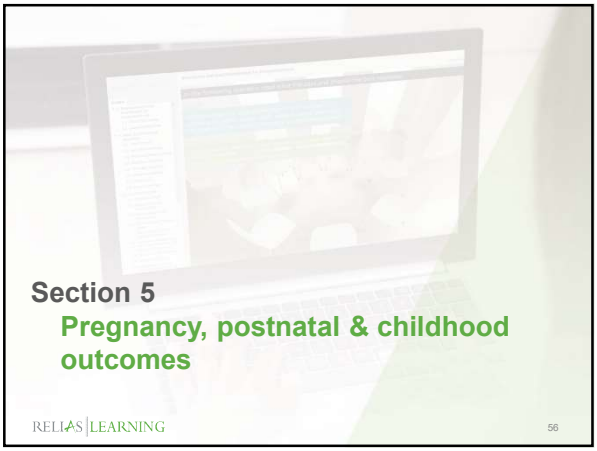
Immunity

- Little data on the effects of cannabis or cannabinoid-based therapeutics on the human immune system.
- There is insufficient data to draw overarching conclusions concerning the effects of cannabis smoke or cannabinoids on immune competence.
- Regular exposure to cannabis smoke may have anti-inflammatory activity.
- No evidence of an association between cannabis or cannabinoid use and adverse effects on immune status in individuals with HIV.



Section 5
Pregnancy, postnatal & childhood outcomes

Pregnancy: Postnatal and Childhood Outcomes

- Smoking cannabis during pregnancy is linked to lower birth weight in the infant.
- The relationship between smoking cannabis during pregnancy and childhood outcomes includes deficits in teacher ratings of learning, memory and impulsivity, as well as depression during 10 year follow-up.
- Children also have impaired executive functioning in maintaining attention and visual analyses.

Section 6
Injury and Death

HEALTH DRUGS

How Much Does Marijuana Impact Your Driving?

Injury and Death

- Cannabis use prior to driving increases the risk of being involved in a motor vehicle accident.
- In states where cannabis use is legal, there is increased risk of unintentional cannabis overdose injuries among children.
- It is unclear whether and how cannabis use is associated with all-cause mortality or with occupational injury.

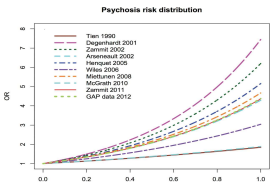
Injury Mechanisms with Cannabinoids

- Combination of THC and alcohol in humans may result in increased levels of THC
- Due to ethanol-induced increases in THC absorption,
- Resulting in enhanced subjective effects and driving impairment

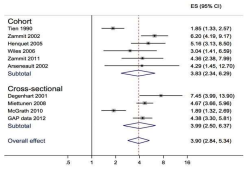
Section 7
Mental Health
Psychosocial outcomes
Problem Cannabis Use

Mental Health

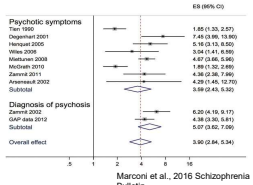
There is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.



A. By study design



B. By outcome measure



Marconi et al., 2016 Schizophrenia Bulletin

Mental Health (1)

- Cannabis use is associated with the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.
- Marijuana induced psychosis is usually brief, but presaged further psychotic episodes in 77% & a full schizophrenia-spectrum disorder in 45% of those having an acute psychosis (Arendt et al., 2005) (Denmark)
- Male cannabis using schizophrenics age at first psychotic episode is 7 years younger than in non-users (Veen, et al., 2004) (Netherlands)
- In schizophrenics, cannabis use may be linked to better performance on learning and memory tasks.

Mental Health (2)

- Heavy cannabis users are more likely to report thoughts of suicide than non-users.
- Regular cannabis use is likely to increase the risk for developing social anxiety disorder.
- Bipolar near daily cannabis users have greater symptoms of bipolar disorder than non-users.
- Cannabis use does not appear to increase the likelihood of developing depression, or posttraumatic stress disorder.

Psychosocial Outcomes

- Recent cannabis use impairs the performance in cognitive domains of learning, memory, and attention. Recent use may be defined as cannabis use within 24 hours of evaluation.
- A limited number of studies suggest that there are impairments in cognitive domains of learning, memory, and attention in individuals who have stopped smoking cannabis.
- Cannabis use during adolescence is related to impairments in subsequent academic achievement and education, employment and income, and social relationships and social roles.

Chronic Cannabinoids damage Brain

1. Administration of THC produces dose-dependent Working Memory deficits & PreFrontal Cortex (PFC) damage in normals.
2. Hypo-activity in dorso-lateral PFC (dlPFC) of marijuana users correlates with increased craving.
3. Marijuana users have dlPFC hypo-activity in response to marijuana cues which predicts increased marijuana-related problems 6-months later.
4. Abstinent marijuana users exhibit persistent deficits in decision-making related to hypo-activity in the dlPFC.
5. Abstinent adolescent-onset marijuana users impairments in Working Memory persist for at least 3 months after stopping .

Problem Cannabis Use

- Greater frequency of cannabis use increases the likelihood of developing problem cannabis use.
- Initiating cannabis use at a younger age increases the likelihood of developing problem cannabis use.

Cannabis Use and Abuse of Other Substances

- There is limited evidence of a statistical association between cannabis use and the initiation of tobacco use.
- There is limited evidence of a statistical association between cannabis use and changes in the rates and use patterns of other licit and illicit substances.
- There is moderate evidence of a statistical association between cannabis use and the development of substance dependence and/or a substance abuse disorder for substances including, alcohol, tobacco, and other illicit drugs.

Section 7
Cannabinoid Withdrawal & Treatment

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Cannabinoid Withdrawal

Signs and symptoms 1 week after stopping:

1. Irritability, anger, or aggression
2. Nervousness or anxiety
3. Sleep difficulty (e.g., insomnia, disturbing dreams)
4. Decreased appetite or weight loss
5. Restlessness
6. Depressed mood
7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headaches

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RELIAS | LEARNING

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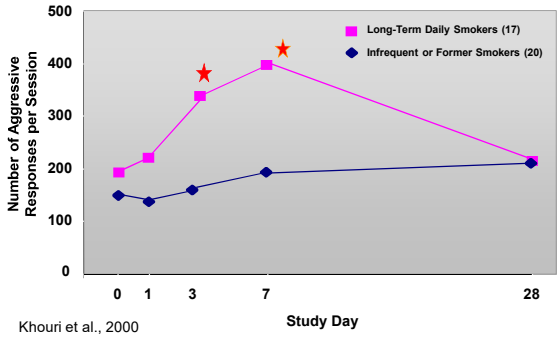
Abstinence Elicits Aggressive Behavior in Long-Term Marijuana Smokers



Khouri et al., 2000

RELIAS | LEARNING
RELIAS | LEARNING

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Cannabinoid Antagonist: Treatment?

- SR 141716 (Rimonabant) blocks CB1 in humans (Huestis et al., 2001)
- An inverse agonist & antagonist
- Partially blocks THC effects
- Precipitates acute & severe withdrawal in THC dependent rats
- Reduces nicotine withdrawal

Treatment of Marijuana Withdrawal

Negative studies:

- Bupropion (Haney et al., 2001) and divalproex (Levin et al., 2003) (Haney et al., 2004) worsen withdrawal
- Nefazodone decreased withdrawal anxiety but not craving (Haney et al, 2003)
- Marinol (synthetic THC) decreased withdrawal (Haney et al, 2004) & positive effects of smoked THC (Hart et al, 2002)
- Sativex (aerosol of THC + cannabidiol) may be better than Marinol when available

Sleep & Cannabis Withdrawal: Guanfacine

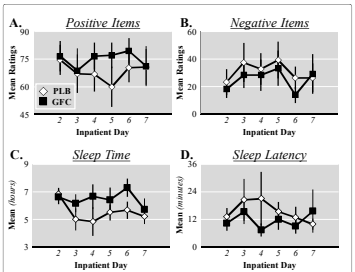


Figure 5. Mean ratings from the Sleep Questionnaire [(**A**) 4-positive items (*top, left*); and (**B**) 2-negative items (*top, right*)] as well as mean (**C**) total sleep time (*bottom, left*); and (**D**) latencies to fall asleep (*bottom, right*) across 5 days (days 2-6) of supervised withdrawal from cannabis during the placebo (PLB) and guanfacine (GFC) treatment arms. Means ± standard errors.

Preventing Marijuana Relapse

- 71% of marijuana dependent patients relapse within 6 months after achieving 2 weeks of abstinence (Moore & Budney, 2003)
- Naltrexone 50 mg. increased MJ intoxication
- Divalproex not effective
- CB-1 antagonist will have compliance problems
- Combining Marinol + Lofexidine to prevent reinstatement looks promising

Barriers to Cannabis Research

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabinoid research.
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on its health effects.
- A diverse network of funders is needed to support cannabinoid research and explore the beneficial and harmful health effects of cannabis use.
- Improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed.

Cannabis in Healthcare – Summary

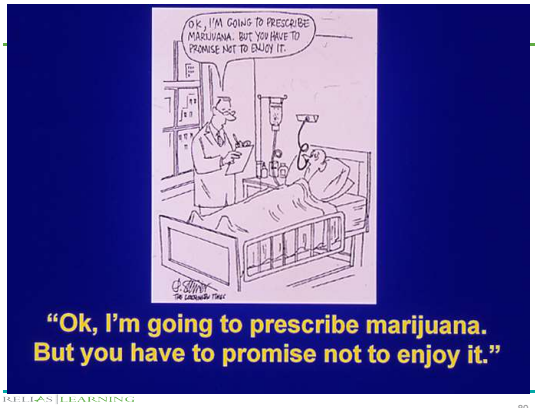
1. Changing Epidemiology & Pharmacology:
   - Fear of harm dropped and **use** rose over past 40 years
   - Synthetic cannabinoids have more toxicity than THC
2. Therapeutic effects:
   - Pain, Vomiting, Spasticity in MS
3. Cancer:
   - Testicular germ cell tumors,
   - NOT lung or ENT CA
4. Respiratory & Cardio-metabolic risks & Immune function:
   - YES- bronchitis, COPD;
   - NO- heart or immune disease
5. Postnatal & Childhood outcomes:
   - Lower birth weight
   - Cognitive deficits in early schooling

Cannabis in Healthcare – Summary (continued)

5. Injury and death: Car accidents & Child overdoses
6. Mental health:
   - More Suicide, schizophrenia, bipolar, social anxiety
   - Psychosocial outcomes: Impair learning, memory, attention
   - Problem cannabis use: Earlier age at onset, lead to substance abuse generally

TREATMENT

1. Withdrawal after stopping cannabinoids is delayed & long & can precipitate aggression
2. Medications have limited efficacy: ? Guanfacine
3. Preventing relapse critical – antagonist & suicide risk



THANK YOU

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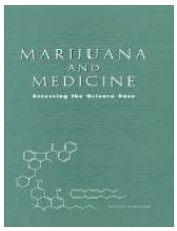
Questions?

References: Classic Reports

Marijuana and Health
(1982)



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