Key Mental and Physical Impacts of Marijuana and the Gene-Environment Debate

Christine L. Miller, Ph.D.

$\Delta^9$ – THC, the psychoactive component of marijuana

Cannabidiol, a non-psychoactive component of marijuana

Anandamide, a human endocannabinoid

Structural and functional differences
The two primary receptors: CB1 and CB2 (the lower the number, the more potent is its activity at that receptor)

$\Delta^9$-THC has more activity at CB1; cannabidiol has more activity at CB2 AND are often functional opposites

Binding affinities and functional activities of all compounds isolated from *Cannabis sativa*. All compounds evaluated displayed agonistic activity in the GTP$_\gamma$S functional assay for both CB1 and CB2 receptors.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Binding Affinity (nM)</th>
<th>Functional Activity (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CB1</td>
<td>CB2</td>
</tr>
<tr>
<td>$\Delta^9$-THC</td>
<td>18 ± 4</td>
<td>42 ± 9</td>
</tr>
<tr>
<td>$\Delta^9$-tetrahydrocannabinolic acid</td>
<td>1292 ± 89</td>
<td>1650 ± 163</td>
</tr>
<tr>
<td>$\Delta^9$-tetrahydrocannabinvarin</td>
<td>22 ± 5</td>
<td>105 ± 21</td>
</tr>
<tr>
<td>Cannabichromanone C</td>
<td>8681 ± 1404</td>
<td>5789 ± 685</td>
</tr>
<tr>
<td>Cannabichromanone D</td>
<td>7117 ± 1090</td>
<td>2828 ± 569</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>151 ± 28</td>
<td>4582 ± 613</td>
</tr>
<tr>
<td>Cannabidivarin</td>
<td>503 ± 58</td>
<td>3970 ± 976</td>
</tr>
</tbody>
</table>

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial

Cannabidiol: efficacy for intractable seizures?

Key points from clinical trial in 2015:

- Cannabidiol was in addition to the anticonvulsant medication the patients were already on
- 2 out of every 5 patients experienced a 50% or greater reduction in seizure frequency, with 2 out of 100 becoming free of seizures; the remainder experienced either less reduction, no change or a seizure increase
- Common adverse events included somnolence, loss of appetite, diarrhea and fatigue
- The most serious adverse event was status epilepticus (continuous seizures) in 6 out of 100 who were treated
Critiques (May 2016) written to Lancet Neurology on the 2015 cannabinoid trial

- The study authors did not highlight that although 1/3rd of the patients exhibited significant improvement, roughly 1/3rd of the patients treated with cannabinoid experienced an increase in seizures.

- The pre-treatment period (4 weeks) was too short to accurately determine the baseline seizure frequency which can vary month to month.

- 30% experienced serious adverse events, a high rate for anticonvulsant treatment.

- The cannabinoid treatment was in addition to other anticonvulsants: the patients were already on, and the metabolism of these other drugs is inhibited by cannabinoid causing an increase in their concentration.
Cannabidiol: efficacy for intractable seizures?

**Mechanism of action in question**

Gaston TE, et al. *Interactions between cannabidiol and commonly used antiepileptic drugs.* Epilepsia. 2017;58(9):1586-1592

*Note the abstract of this paper requires clarification: the reason the clobazam level decreased as the investigators increased the cannabidiol dose is that the dose of clobazam was proactively lowered as a safety precaution.

Cannabidiol increases levels of other anticonvulsants to values outside the therapeutic range

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### Table 3. Quantification of AED level changes

<table>
<thead>
<tr>
<th>AED level</th>
<th>N</th>
<th>Mean baseline level</th>
<th>Mean first “on CBD” level</th>
<th>Mean second “on CBD” level</th>
<th>Normal AED level range (trough)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clobazam(^a)</td>
<td>27</td>
<td>264.7 ± 136.3</td>
<td>331.1 ± 143.2 (dose unchanged)</td>
<td>310.9 ± 104.2 (dose unchanged)</td>
<td>30–300 ng/ml</td>
</tr>
<tr>
<td>N-desmethylclobazam(^a)</td>
<td>26</td>
<td>2,207.5 ± 1,854.0</td>
<td>3,727.7 ± 1,549.3 (dose unchanged)</td>
<td>3,696.8 ± 1,027.1 (dose unchanged)</td>
<td>300–3,000 ng/ml</td>
</tr>
<tr>
<td>Eslicarbazepine(^b)</td>
<td>4</td>
<td>14.4 ± 7.4</td>
<td>16.8 ± 7.9</td>
<td>17.8 ± 9.1</td>
<td>2–28 µg/ml</td>
</tr>
<tr>
<td>Topiramate</td>
<td>20</td>
<td>10.3 ± 5.9</td>
<td>10.8 ± 7.0</td>
<td>11.3 ± 8.3</td>
<td>4.5–20 µg/ml</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>14</td>
<td>17.2 ± 12.2</td>
<td>19.3 ± 13.0</td>
<td>17.2 ± 9.3 (dose unchanged)</td>
<td>42.0 (dose decreased in 1 adult)</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>14</td>
<td>24.8 ± 12.8</td>
<td>25.6 ± 13.6</td>
<td>27.0 ± 14.7 (dose unchanged)</td>
<td>12.2 (dose decreased in one child)</td>
</tr>
</tbody>
</table>

AED levels that were identified to have statistically significant changes in the presence of CBD were further analyzed to determine the degree in change of AED level over time from pre-CBD baseline to the first two blood levels after the initiation of CBD. Due to the naturalistic study design, CBD dose was not accounted for in this analysis. AEDs marked with an asterisk (clobazam p < 0.030, desmethylclobazam p < 0.001, and eslicarbazepine p = 0.008, marked with \(^b\)) showed a statistically significant increase in mean level with the presence of CBD between the baseline and presented in the table time point. Discrepancies in number of participants between Table 2 and here are due to lack of baseline N-desmethylclobazam in one participant, and lack of follow-up rufinamide levels in two participants due to quick withdrawal from the study.
Cannabidiol: efficacy for intractable seizures?

Studies of cannabidiol in 3 different animal models as a stand-alone treatment.

Yes

"Here we show that cannabidiol (CBD) effectively reduced seizures and autistic-like social deficits in a well-validated mouse genetic model of Dravet syndrome (DS), a severe childhood epilepsy disorder caused by loss-of-function mutations in the brain voltage-gated sodium channel Nav 1.1“

Yes

"CBD (cannabidiol; 30 mg/kg) pre-treatment increased the latency and reduced the duration of cocaine (75 mg/kg)-induced seizures in mice ......CB1 and CB2 antagonists failed to block cannabidiol's effects” Thus, in this type of seizure model, cannabidiol is exerting its anticonvulsant effects through a mechanism that does not involve the traditional cannabinoid receptors.

Yes

“Pretreatment with CBD (60mg/kg) attenuated seizures induced by intraperitoneal, subcutaneous, and intravenous PTZ administration in mice. The effects were reversed by CB1, CB2, and TRPV1 (capsaicin receptor) selective antagonists (AM251, AM630, and SB366791, respectively). Additionally, CBD delayed seizure sensitization resulting from repeated PTZ administration (kindling)...... In conclusion, the robust anticonvulsant effects of CBD may result from multiple pharmacological mechanisms, including facilitation of endocannabinoid signaling and TRPV1 mechanisms.” Cannabidiol injected i.p.
Key points from this most recent clinical trial:

- **Cannabidiol was in addition to** the medication the patients were already on.
- **Patients treated with cannabidiol were twice as likely to experience a 50% reduction** in convulsive seizure frequency as those on placebo.
- **Cannabidiol was ineffective for non-convulsive seizures** (e.g. “absence seizures” or staring seizures).
- **One out of twenty** of the cannabidiol-treated patients became seizure-free as compared to none who were on placebo.
- **Approximately one out of ten** cannabidiol-treated patients experienced an increase in convulsions, about twice the rate of the placebo group.
- **The number of patients** who developed status epilepticus was the same in the cannabidiol and placebo groups.
Gastric fluid degraded 98% of the cannabidiol via acid-catalyzed reactions within 2 hours. One of the major products of the degradation was Δ⁹-THC, which reached levels capable of exerting physiological effects.

Therefore, sublingual administration should be considered (though difficult for children), because saliva is not acidic as compared to gastric fluid.
Immune system suppression by cannabinoids: a benefit for the spasticity of multiple sclerosis?

Current drugs are ineffective, difficult to administer, or have undesirable side effects: baclofen, dantrolene, diazepam, tizanidine, botulinum toxin

**Human studies**

**Yes, but subjectively measured**


**Oral administration:** "Pain was significantly reduced when measured directly after administration...a similar pattern was observed in subjective muscle spasticity....One third (n=4) of the patients treated (with oral Δ⁹-THC ) reported muscular weakness during the treatment phase. This muscular weakness may be a part of the causal pathway of reduced muscle tension, leading to the intended treatment of spasticity...... The discrepancy between the objective and subjective measures of spasticity seen in the study has previously also has been observed....spasticity and pain appear to be influenced by Δ⁹-THC through higher-level central nervous system modulation of perception of spasticity rather than electrophysiologic muscle spasticity itself.”

**Yes, but subjectively measured**


**Oral administration:** "611 of 630 patients were followed up for the primary endpoint. We noted no treatment effect of cannabinoids on the primary outcome (as objectively measured by the Ashworth scale)" however "There was evidence of a treatment effect on patient-reported spasticity and pain (p = 0.003)."
Immune system suppression by cannabinoids: a benefit for the spasticity of multiple sclerosis? (continued)

**Human studies**

**Administration via smoking:** “Treatment with smoked cannabis resulted in a reduction in patient scores on the modified Ashworth scale by an average of 2.74 points more than placebo (p<0.0001). In addition, treatment reduced pain scores on a visual analogue scale by an average of 5.28 points more than placebo (p=0.008)...Scores on the Paced Auditory Serial Addition Test decreased by 8.67 points more with treatment than with placebo (p = 0.003).” With smoked marijuana, objective measures of spasticity and pain were improved; however, meaningful functional changes were less clear as the timed walk was not significantly improved, and cognition as measured in an addition test was negatively affected by the end of the 11-day treatment period. The study was placebo-controlled, with placebo cigarettes provided by NIDA. The placebo cigarette is produced from solvent extraction of the dried marijuana plant material, much like the process used for decaffeination of coffee by some manufacturers. However, smoked marijuana impairs posture and balance in patients with spasticity (Koppel et al., Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders. Neurology. 2014 Apr 29;82(17):1556-63.)

**Safety study, some side effects**

A study of the safety profile (not efficacy) of oral administration: "The object of this study was to monitor the safety.. of long-term use of an oromucosal cannabis-based medicine in patients with multiple sclerosis." The drug delivery was oral. Most unwanted effects were mild to moderate: oral pain, dizziness, diarrhea, nausea and oromucosal disorder, but four patients (out of 137) had first-ever seizures, one of whom died from aspiration pneumonia.
“These results suggest that cannabis use in MS results in more widespread cognitive deficits, which correlate with tissue volume in subcortical, medial temporal, and prefrontal regions. These are the first findings demonstrating an association between cannabis use, cognitive impairment and structural brain changes in MS patients.” Roughly half the subjects smoked marijuana at least weekly, most of those daily. It should be noted the cannabidiol content of the marijuana was unknown, but likely quite low.

“Cannabinoid treatment did not induce psychopathology and did not impair cognition in cannabis-naive patients with MS. However, the positive correlation between blood levels of Δ⁹-THC and psychopathological scores suggests that at dosages higher than those used in therapeutic settings, interpersonal sensitivity, aggressiveness, and paranoiac features might arise, although greater statistical power would be necessary to confirm this finding.” The Δ⁹-THC and cannabidiol were administered by sublingual spray, in modest doses (2.7 mg Δ⁹-THC and 2.5 mg cannabidiol), which were allowed ad lib, reaching a mean of 8.2 doses per day or a total of 22 mg Δ⁹-THC and 20.5 mg cannabidiol.
Animal studies

"Chronic relapsing experimental allergic encephalomyelitis is an autoimmune model of multiple sclerosis....Here we show that cannabinoid (CB) receptor agonism using R(+)·WIN 55,212; Δ9-tetrahydrocannabinol; methanandamide and JWH-133 quantitatively ameliorated both tremor and spasticity in diseased mice.” The drugs were preferentially active at the CB1 receptor except for JWH-133, which is preferentially active at CB2.

“Sativex (10 mg/kg) was just as effective as baclofen, providing supportive evidence for Sativex use in the treatment of spasticity in MS.”

Yes

Yes
Immune system suppression by cannabinoids: increases risk for some infections?

Yes


“The preponderance of studies to date indicates that the cannabinoid receptor that is linked to modulation of the majority of immune functional responses is the CB2. A number of reports have indicated that cannabinoids suppress the antibody response of humans and animals.”

Yes


Infections, animal studies

“In our studies, THC pretreatment of mice infected with (*Legionella pneumophila*) affects both innate immunity and the development of the adaptive (cell-mediated) immune response.”
Immune system suppression by cannabinoids – risk of infections?

**Animal studies**

"Collectively, these results suggest that ∆9-THC treatment increased viral load...through a decrease in recruitment of macrophages and lymphocytes"

**Human studies**

“In conclusion, daily cannabis smoking is significantly associated with fibrosis progression during CHC (chronic hepatitis C). Patients with ongoing CHC should be advised to refrain from regular cannabis use.” However, a longitudinal study does not support this conclusion: Brunet L, Marijuana smoking does not accelerate progression of liver disease in HIV-hepatitis C coinfection: a longitudinal cohort analysis. Clin Infect Dis. 2013;57(5):663-70. The Brunet et al. study did not find an acceleration of cirrhosis in users for recent marijuana use, but when they considered current marijuana use, the risk for cirrhosis was 33% higher.

**Yes**


**Yes**


**Yes**


“Frequent cannabis use is associated with symptoms of bronchitis in young adults. Reducing cannabis use often leads to a resolution of these symptoms.”
**Neuropathic pain**: the sensory fibers themselves are dysfunctional or irritated, sending incorrect signals to pain centers

**Yes, somewhat**


**Human studies**: “Selective cannabinoids (Δ⁹-THC and/or cannabidiol) provide a small analgesic benefit in patients with chronic NP (neuropathic pain)…Similar to selective cannabinoids, escalation in strength of THC for cannabis has not been clearly demonstrated to provide superior analgesia and resulted in worsened neuropsychological performance”

**Yes, somewhat**


**Human studies**: “Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients.”

**Yes, esp. cannabidiol**


**Animal study**: “CBD (cannabidiol) may be potent and effective at preventing the development of chemotherapy-induced peripheral neuropathy, and its clinical use may be enhanced by co-administration of low doses of THC.”
Marijuana for Pain?

Human studies, mixed types of pain: both neuropathic and non-neuropathic (nociceptive)

No

Shah et al., *Medical cannabis use among patients with chronic pain in an interdisciplinary pain rehabilitation program*: Characterization and treatment outcomes. J Subst Abuse Treatment 2017; 77:95-100

Marijuana may not decrease the amount of opiates needed: “Cannabis use was not associated with a significantly lower morphine equivalence level for participants using prescription opioids (n=14). Both groups of participants reported significant improvement in pain severity, pain interference, depressive symptoms, and pain catastrophizing. There were no group- or treatment-related differences in these outcome variables.”

Yes and No; medium- but not high-dose


Evidence for increased pain at high doses for specific types of pain: “Wallace et al. tested the effects of smoked cannabis (low, medium, or high doses vs. inactive placebo) on intradermal capsaicin-induced pain responses using a randomized, double-blind, crossover trial in 15 healthy volunteers (mean age of 28.9; 58% male). Results indicated a significant decrease in pain with the medium cannabis dose and a significant increase in pain with the high dose.” and some evidence for increased pain at all doses for sunburn: “There was also some evidence of an unexpected hyperalgesic state in the cannabis group.”...”Pre-clinical studies demonstrate a narrow therapeutic window for cannabis “. 
**Nociceptive Pain**: caused by damage to body tissue and usually described as a sharp, aching, or throbbing pain.

**No**


**Human studies**: “Contrary to our hypothesis, *THC did not show a beneficial effect on chronic abdominal pain* compared with placebo. Similar results were observed for minimal and maximal reported VAS pain (subjective scoring of pain by patient), indicating that THC does not affect background pain or pain peaks.”

**No**


**Human studies**: “*Sativex (THC+CBD) did not demonstrate superiority to placebo in reducing self-reported pain scores in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy*”

**Yes for THC, No for CBD alone**


**Animal study**: “*CBD (cannabidiol) alone produced no antinociceptive effects... may enhance THC's antinociceptive and hypolocomotive effects, primarily prolonging THC's duration of action.*”
Animal study: **novel (allosteric) drugs** enhancing cannabinoid receptor function for pain

Yes


“Therapeutic efficacy was preserved over 19 days of chronic dosing...shows promise as a safe and effective analgesic (pain relief) strategy that lacks tolerance, dependence and abuse liability.” **Positive allosteric modulators:** the length of time for therapeutic efficacy is better than that seen for CB1 agonists.
Marijuana for Pain: substitution for opiates?

**Human studies**

**Yes**
Corroon JM, et al. **Cannabis as a substitute for prescription drugs - a cross-sectional study.** J Pain Res. 2017 May 2;10:989-998

"Individuals (some recreational users) are substituting cannabis for prescription drugs, independent of whether they identify themselves as medical users and independent of legal access to medical cannabis... the most common classes of substitution were narcotics/opioids, anxiolytics/benzodiazepines and antidepressants“ Data was obtained from response to questionnaires, not clinical interviews; no monitoring of actual prescription fill-rate for the medical patients.

**No**

"Cannabis use was not associated with a significantly lower morphine equivalence level for participants using prescription opioids.... Prescription opioid use was established based on a clinical interview with a pharmacist"

**No**
Smaga S and Gharib AMR. **In adults with chronic low back pain, does the use of inhaled cannabis reduce overall opioid use?** Evidence Based Practice 2017; 20(1):e10

A small review, reporting studies show on average higher use of opiates in those who use cannabis for pain: “Persons who used cannabis for pain used a median oral morphine equivalent dose of 100 mg/d compared with 69 mg/d in those who did not use cannabis for pain.....Persons using cannabis for pain were more likely to meet criteria for substance abuse disorders (alcohol abuse disorder OR 6.3...amphetamine use disorder OR 6.3..... illicit opioid use disorder OR 4.3)”
"Concurrent use of cannabis and opioids by patients with chronic pain appears to indicate higher risk for opioid misuse."
Marijuana for Pain: substitution for opiates?

No

Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States

Mark Ofson, M.D., M.P.H., Melanie M. Wall, Ph.D., Shang-Min Liu, M.S., Carlos Blanco, M.D., Ph.D.

Objective: The authors sought to determine whether cannabis use is associated with a change in the risk of incident nonmedical prescription opioid use and opioid use disorder at 3-year follow-up.

Method: The authors used logistic regression models to assess prospective associations between cannabis use at wave 1 (2001–2002) and nonmedical prescription opioid use and prescription opioid use disorder at wave 2 (2004–2005) of the National Epidemiologic Survey on Alcohol and Related Conditions. Corresponding analyses were performed among adults with moderate or more severe pain and with nonmedical opioid use at wave 1. Cannabis and prescription opioid use were measured with a structured interview (the Alcohol Use Disorder and Associated Disabilities Interview Schedule—DSM-IV version). Other covariates included age, sex, race/ethnicity, anxiety or mood disorders, family history of drug, alcohol, and behavioral problems, and, in opioid use disorder analyses, nonmedical opioid use.

Results: In logistic regression models, cannabis use at wave 1 was associated with increased incident nonmedical prescription opioid use (odds ratio = 5.78, 95% CI = 4.23–7.90) and opioid use disorder (odds ratio = 7.76, 95% CI = 4.95–12.16) at wave 2. These associations remained significant after adjustment for background characteristics (nonmedical opioid use: adjusted odds ratio = 2.62, 95% CI = 1.86–3.69; opioid use disorder: adjusted odds ratio = 2.18, 95% CI = 1.14–4.14). Among adults with pain at wave 1, cannabis use was also associated with increased incident nonmedical opioid use (adjusted odds ratio = 2.99, 95% CI = 1.63–5.47) and opioid use disorder, although the association fell short of significance (adjusted odds ratio = 2.14, 95% CI = 0.95–4.83). Among adults with nonmedical opioid use at wave 1, cannabis use was also associated with an increase in nonmedical opioid use (adjusted odds ratio = 3.13, 95% CI = 1.19–8.23).

Conclusions: Cannabis use appears to increase rather than decrease the risk of developing nonmedical prescription opioid use and opioid use disorder.

"cannabis use at wave 1 was associated with increased incident nonmedical prescription opioid use (odds ratio = 5.78) and opioid use disorder (odds ratio = 7.76). These associations remained significant after adjustment for background characteristics."
But is there evidence that medical marijuana states may have lower rates of opiate overdoses? Not really.

Overdose deaths have continued to rise across the nation, and states with medical marijuana laws have consistently shown higher rates of opioid overdoses, unless correction factors are applied. Bachhuber et al. applied correction factors which they term “state-specific” (an approach used by economists, not epidemiologists) without identifying what those factors were, and after the correction (data not shown in figure form) found that medical marijuana states had lower overdose rates, erasing the difference seen in the graph below. An example of inappropriate correction would be correcting for measures correlating with how “progressive” a state was (see “collider” variables later on).

The authors further found that “medical cannabis laws were associated with lower rates of opioid analgesic overdose mortality, which generally strengthened in the years after passage.” Yet, the authors did not examine actual medical marijuana prescribing rates, or patient registration numbers, which often did not steadily increase over time. In Colorado, for example, a substantial rise in registered medical marijuana patients was delayed, undergoing an exponential increase 8 years post-enactment of medical marijuana.
Marijuana for Pain: substitution for opiates?

This recent study found: “Legalization of cannabis in Colorado was associated with short-term reductions in opioid-related deaths”

But, the Colorado Department of Public Health had this to say about the study:

"In addition to the stronger (prescription opioid) monitoring program, 2014 also saw increased public education about the dangers of opioid prescribing and wider distribution of the overdose-reversing drug naloxone. The Colorado Consortium for Prescription Drug Abuse Prevention, which brings doctors, pharmacists, policy officials and others together, was also just getting up to speed...Valuck also noted that, even as prescription opioid deaths have fallen, deaths from heroin have been rising in Colorado - meaning it is possible that what appears to be progress in combating prescription drug addiction is actually just a large-scale switch to a different opiate."
The special case of the lung: evidence for lung cancer risk is not strong

1. “Currently, the evidence regarding an **association of cannabis smoking and lung cancer is inconclusive**” (Ribeiro LI, Ind PW. Effect of cannabis smoking on lung function and respiratory symptoms: a structured literature review. NPJ Prim Care Respir Med. 2016;26:16071).

2. However, marijuana smoking may **potentiate risk for COPD** in cigarette smokers, but may not increase risk by itself (Tan WC, et al. Marijuana and chronic obstructive lung disease: a population-based study. CMAJ. 2009;180(8):814-20)

Doubles Risk of Testicular Cancer

Lackson et al., 2012, Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. Cancer 188:5374-83. “Compared to never use, ever use of marijuana had a 2-fold increased risk”. The data were adjusted for a history of cryptorchidism, which by itself confers a high risk.

Trabert et al., 2011, Marijuana use and testicular germ cell tumors. Cancer 117:848-53. “Overall, patients with TGCTs were more likely to be frequent marijuana users (daily or greater) compared with controls (odd ratio [OR] 2.2).” The analyses were adjusted for age, time of interview, race, history of cryptorchidism, tobacco use and alcohol use.

Daling JR, et al. 2009, Association of marijuana use and the incidence of testicular germ cell tumors. Cancer;115(6):1215-23. “Men with a TGCT were more likely to be current marijuana smokers at the reference date compared with controls (odds ratio [OR] 1.7).” The analyses were adjusted for age, reference year, history of cryptorchidism, first-degree family history of TGCT (testicular germ cell tumors), race and income.
Animal studies: “Phytocannabinoids such as Δ⁹-THC and CBD induce breast cancer regression and progression in vivo, indicating that a complex interaction between these compounds and cancer exists.” The breast cancer progression with THC was observed in immunocompetent mice. But for CBD: McCallister et al. (2011) “Using immune competent mice, we then show that treatment with CBD (cannabidiol) significantly reduces primary (breast) tumor mass as well as the size and number of lung metastatic foci” (Breast Cancer Res. Treat. 129(1):27-37).

Breast cancer:

Animal and human studies: “Numerous studies indicate that Δ⁹-THC is a potent inducer of glioma death in vivo” However, none of those studies involved immunocompetent mice, and none showed eradication of the tumors. Furthermore, there may be a biphasic effect with stimulation of glioma growth at low concentrations and inhibition of glioma growth at high concentrations of Δ⁹-THC (see later slide). Furthermore: Efird et al. (2004) found that risk for glioma was increased 2.8-fold in those who smoked marijuana at least once per month, after correcting for cigarette smoking and other factors (J. Neuro-oncology 68:57-69).
Prostate cancer: “Cannabis extracts enriched with CBD (cannabidiol) effectively decreased tumor growth in androgen-receptor-positive LNCaP xenografts but potentiated tumor growth of androgen-receptor-negative DU-145 xenographs” However, none of those studies involved immunocompetent mice.

Animal studies: “Cannabis extracts enriched with CBD (cannabidiol) effectively decreased tumor growth in androgen-receptor-positive LNCaP xenografts but potentiated tumor growth of androgen-receptor-negative DU-145 xenographs” However, none of those studies involved immunocompetent mice.

Lung cancer: CB1 and CB2 are opposed.

Animal and human studies: “Preet et al. found that the phytocannabinoid, ∆9-THC, downregulated Akt in A549-driven xenografts, which corresponded with decreased tumor growth and metastasis….In contrast, Zhu et al. showed that ∆9-THC increased the tumorigenicity of 3LL lung cancer cells in allografted immunocompetent mice and demonstrated that CB2 mediated inhibition of anti-tumor lymphocyte activity was the primary mechanism for accelerated tumor growth……Consequently, several of these studies indicate that anti-tumor immunity is suppressed by certain cannabinoids, exacerbating tumor growth in immune-competent animals.” In human epidemiological studies, Zhang et al. 2014 found risk for adenocarcinoma of the lung increased by 1.74-fold in daily marijuana users after correcting for tobacco use, but risk for other types of lung cancer was decreased (Int. J. Cancer 136:894-903), such that overall risk was not increased. A Swedish study found overall risk for lung cancer was more than doubled by 50 or more times of use (Callaghan et al., 2013, Cancer Causes and Control, 24(10):1811-20), after statistically adjusting for tobacco use, alcohol use, respiratory ailments and socioeconomic status. Although this study is large, there are significant flaws in its methodology that limit the conclusions that can be drawn. The subjects were only assessed for tobacco and cannabis use at the time of conscription with no information on use patterns before conscription and the 40 years after conscription.
Continued....

**Liver cancer:**

Animal studies: “Xu et al. found that the expression of both CB1 and CB2 receptors was increased in hepatomas and was strongly associated with improved prognosis and disease-free survival rates. Conversely, Mukhopadhyay et al. reported that CB1 receptors promote the initiation and progression of diethylnitrosamine-induced hepatomas in mice.”

Δ⁹-THC partially activates CB1 and CB2 Suk et al. 2016: “**Opposite roles of cannabinoid receptors 1 and 2 in hepatocarcinogenesis**”......”inactivation of CB1..suppressed hepatocarcinogenesis. In contrast, inactivation of CB2 increased hepatocarcinogeneisis”

**Colorectal cancer:**

Animal studies: “In chemically-induced...colon carcinogenesis, the phytocannabinoids, CBD and Cannabis sativa extract (which contains high CBD...) reduced aberrant crypt foci formation and the number of precancerous polyps and tumors.”

These experiments were conducted in immunocompetent animals. However, the CBD effect may be biphasic, stimulating colorectal cancer at low concentrations and inhibiting at high concentrations (*see later slide*).
Pancreatic cancer: CB1 and CB2 are opposed

Animal studies: “high levels of CB1 receptor expression......were associated with shorter survival...In vitro studies showed that the anti-proliferative activity of the cannabinoids was mediated by the activation of CB2 receptors.”

Melanoma: CB1 and CB2 are opposed

Animal studies: “The anti-tumor activity of cannabinoids was mediated by CB2 receptor activation” However, all of the work was conducted in vitro or in immunocompromised animals. Carpi et al. (2017) “The tumor-promoting effects of cannabinoid receptor type 1 in human melanoma cells” (Toxicology In Vitro, in press). Their cellular model involved physically eliminating CB1, which eliminated tumor progression. “Such an approach may offer some advantages over functional studies using selective CB1 receptor agonists and antagonists because these compounds may also act through off-target mechanisms, which can make data interpretation difficult and ambiguous.”
low concentrations of ∆⁹-THC promoted tumor growth. However, in the presence of high ∆⁹-THC concentrations, ∆⁹-THC inhibited tumor cell growth.” This biphasic pattern may reflect ∆⁹-THC binding better to CB2 at high concentrations.

But even for drugs more specific for CB2, biphasic effect seen: “The proliferation increased until 1μM, while 10 μM decreased cell survival, resulting in a biphasic proliferation curve” Martinez-Martinez et al., 2016: CB2 receptor activation promotes colon cancer progression… (at) submicromolar doses of agonists, (which are) more similar to endogenous levels of cannabinoids”.

The problem of the biphasic response to phytocannabinoids:
This biphasic effect may represent evidence of differential receptor binding, where at low doses the drug binds to receptors that possess high affinity, and at high doses to other receptors with lower affinity.

Glioblastoma:
“low concentrations of ∆⁹-THC promoted tumor growth. However, in the presence of high ∆⁹-THC concentrations, ∆⁹-THC inhibited tumor cell growth.” This biphasic pattern may reflect ∆⁹-THC binding better to CB2 at high concentrations.
Marijuana and Cancer: GPR55 as a Potential Reason for Variable Effects of THC

THC activates, cannabidiol inhibits GPR55: a non-traditional receptor for phytocannabinoids


In vitro: GPR55 - activation would be expected to increase cancer progression.


In vitro: “Δ⁹-THC activated (this receptor)...binding with an EC50 of 8 nM”. Therefore, THC is a very potent activator of this cancer-promoting receptor. “However, cannabidiol was able to antagonize the agonist effect ... with an IC50 of 445 nM”. Thus, cannabidiol is a modestly potent antagonist of this receptor.
New, potentially more specific cannabinoid drugs in the pharmaceutical pipeline

WIN55-212-2, specificity for activation of CB1 and CB2, effective in reducing cancer cell proliferation
CP55,940, specificity for activation of CB1 and CB2, effective in reducing cancer cell proliferation

JWH018, a selective CB1 agonist, component of blends of the street drug “spice”
ACEA, a selective CB1 agonist, potentiates some anticonvulsants but diminishes efficacy of others
ACPA, a selective CB1 agonist, impairs cells involved in memory function in the hippocampus
Chromenopyrazole-13a, a selective CB1 agonist that appears blocked by the blood brain barrier

JWH015, a selective CB2 agonist reduced tumor burden in immunocompetent mice
JWH105, preferential CB2 agonist that is effective in reducing cancer cell proliferation
JWH133, a selective CB2 agonist showing mixed results in reducing cancer cell proliferation, biphasic effect
JWH139, a selective CB2 agonist effective in reducing cancer cell proliferation
HU308, a selective CB2 agonist showing mixed results in reducing cancer cell proliferation
HU433, a selective CB2 agonist
AM1241, a selective CB2 agonist effective in reducing cancer cell proliferation
Marijuana use may increase heart complications in young, middle-aged adults

Marijuana use may result in cardiovascular-related complications — even death — among young and middle-aged adults, according to a French study published on Wednesday.

"In prior research, we identified several remarkable cases of cardiovascular complications as the reasons for hospital admission of young marijuana users," said Emilie Jouanjus, Pharm.D., Ph.D., lead author of the study and a medical faculty member at the Centre Hospitalier Universitaire de Toulouse in Toulouse, France. "This unexpected finding deserved to be further analyzed, especially given that the medicinal use of marijuana has become more prevalent and some governments are legalizing its use."

Researchers analyzed serious cardiovascular-related complications following marijuana use that was reported to the French Addictovigilance Network in 2006-10. They identified 35 cases of cardiovascular and vascular conditions related to the heart, brain and limbs.

Among their findings:

- Most of the patients were male, average age 34.3 years;
- Nearly 2 percent (35 of the 1,579) marijuana-related complications were cardiovascular complications;
- Of the 35 cases, 22 were heart-related, including 20 heart attacks. Ten were peripheral with diseases related to arteries in the limbs. Three were related to the brain's arteries;
- The percentage of reported cardiovascular complications more than tripled from 2006 to 2010;
- Nine patients, or 25.6 percent, died.

Researchers note that marijuana use and any resulting health complications are likely underreported.
Marijuana Use and Cardiovascular Disease

Franz, Christopher A. MD; Frishman, William H. MD

Cardiology in Review: July/August 2016 - Volume 24 - Issue 4 - p 158–162

Review Articles

Abstract

Marijuana is currently the most used illicit substance in the world. With the current trend of decriminalization and legalization of marijuana in the US, physicians in the US will encounter more patients using marijuana recreationally over a diverse range of ages and health states. Therefore, it is relevant to review marijuana’s effects on human cardiovascular physiology and disease. Compared with placebo, marijuana cigarettes cause increases in heart rate, supine systolic and diastolic blood pressures, and forearm blood flow via increased sympathetic nervous system activity. These actions increase myocardial oxygen demand to a degree that they can decrease the time to exercise-induced angina in patients with a history of stable angina. In addition, marijuana has been associated with triggering myocardial infarctions (MIs) in young male patients. Smoking marijuana has been shown to increase the risk of MI onset by a factor of 4.8 for the 60 minutes after marijuana consumption, and to increase the annual risk of MI in the daily cannabis user from 1.5% to 3% per year. Human and animal models suggest that this effect may be due to coronary arterial vasospasm. However, longitudinal studies have indicated that marijuana use may not have a significant effect on long-term mortality. While further research is required to definitively determine the impact of marijuana on cardiovascular disease, it is reasonable to recommend against recreational marijuana use, especially in individuals with a history of coronary artery disorders.
Marijuana and the Cardiovascular System

Adverse Cardiovascular, Cerebrovascular, and Peripheral Vascular Effects of Marijuana Inhalation: What Cardiologists Need to Know

Grace Thomas, MDa, Robert A. Kloner, MDh,c, and Shereif Rezkalla, MDa,d,g

Marijuana is the most widely used illicit drug, with approximately 200 million users worldwide. Once illegal throughout the United States, cannabis is now legal for medicinal purposes in several states and for recreational use in 3 states. The current wave of decriminalization may lead to more widespread use, and it is important that cardiologists be made aware of the potential for marijuana-associated adverse cardiovascular effects that may begin to occur in the population at a greater frequency. In this report, the investigators focus on the known cardiovascular, cerebrovascular, and peripheral effects of marijuana inhalation. Temporal associations between marijuana use and serious adverse events, including myocardial infarction, sudden cardiac death, cardiomyopathy, stroke, transient ischemic attack, and cannabis arteritis have been described. In conclusion, the potential for increased use of marijuana in the changing legal landscape suggests the need for the community to intensify research regarding the safety of marijuana use and for cardiologists to maintain an awareness of the potential for adverse effects. © 2014 Elsevier Inc. All rights reserved. (Am J Cardiol 2014;113:187–190)

Temporal associations with:
- Heart attack
- Sudden cardiac death
- Cardiomyopathy
- Stroke
- Transient ischemic attack
- Arteritis
Marijuana and the Cardiovascular System

Triggering Myocardial Infarction by Marijuana

Murray A. Mittleman, MD, DrPH; Rebecca A. Lewis; Malcolm Maclure, ScD; Jane B. Sherwood, RN; James E. Muller, MD

Background—Marijuana use in the age group prone to coronary artery disease is higher than it was in the past. Smoking marijuana is known to have hemodynamic consequences, including a dose-dependent increase in heart rate, supine hypertension, and postural hypotension; however, whether it can trigger the onset of myocardial infarction is unknown.

Methods and Results—In the Determinants of Myocardial Infarction Onset Study, we interviewed 3882 patients (1258 women) with acute myocardial infarction an average of 4 days after infarction onset. We used the case-crossover study design to compare the reported use of marijuana in the hour preceding symptoms of myocardial infarction onset to its expected frequency using self-matched control data. Of the 3882 patients, 124 (3.2%) reported smoking marijuana in the prior year, 37 within 24 hours and 9 within 1 hour of myocardial infarction symptoms. Compared with nonusers, marijuana users were more likely to be men (94% versus 67%, \( P<0.001 \)), current cigarette smokers (68% versus 32%, \( P<0.001 \)), and obese (43% versus 32%, \( P=0.008 \)). They were less likely to have a history of angina (12% versus 25%, \( P<0.001 \)) or hypertension (30% versus 44%, \( P=0.002 \)). The risk of myocardial infarction onset was elevated 4.8 times over baseline (95% confidence interval, 2.4 to 9.5) in the 60 minutes after marijuana use. The elevated risk rapidly decreased thereafter.

Conclusions—Smoking marijuana is a rare trigger of acute myocardial infarction. Understanding the mechanism through which marijuana causes infarction may provide insight into the triggering of myocardial infarction by this and other, more common stressors. (*Circulation. 2001;103:2805-2809.*)

Key Words: cannabis ■ myocardial infarction ■ epidemiology ■ cross-over studies
Marijuana and the Cardiovascular System

Topical Review

Cannabis-related Stroke
Myth or Reality?

Valérie Wolff, MD; Jean-Paul Armispach, PhD; Valérie, Lauer, MD; Olivier Rouyer, MD, PhD; Marc Bataillard, MD; Christian Marescaux, MD; Bernard Geny, MD, PhD

Conclusion
In regard to the literature, cannabis-related stroke is not a myth, and a likely mechanism of stroke in most cannabis users is the presence of reversible MIS induced by this drug. The reality of the relationship between cannabis and stroke is, however, complex because other confounding factors have to be considered (ie, lifestyle and genetic factors).
Cannabis-Related Stroke: Case Series and Review of Literature

Niranjan N. Singh, MD,* Yi Pan, MD, PhD,† Sombat Muengtaweeponsa, MD,‡ Thomas J. Geller, MD,† and Salvador Cruz-Flores, MD†

Marijuana, or cannabis, is one of the most commonly used illicit drugs worldwide. Although there are some case reports of stroke associated with cannabis use, there is no information on a causal role of cannabis in stroke. We identified 14 patients admitted to St Louis University Hospital between January 2004 and July 2007 with ischemic stroke who had documented clear exposure to cannabis during or before symptom onset and a positive urine screen for cannabis. We report this series, along with 3 cases previously reported by our group, for a total of 17 patients (13 men and 4 women), with a mean age of 41 years (range, 15-63 years). Nine patients were under age 45 years, 4 had a history of hypertension, and 10 sustained stroke in the posterior circulation. Headache, dysarthria, and ataxia were the most common presenting symptoms. Five patients had recurrent stroke with reexposure to cannabis. No patient had a prothrombotic state or cardiac source of embolism. Autopsy performed in 2 patients revealed hemorrhagic infarct with no evidence of vasculitis or embolus. The absence of other vascular risk factors in most of our patients, the temporal relation of symptom onset to cannabis exposure, and the recurrence of symptoms in a few patients with reexposure suggest a causal role of cannabis in these cases of ischemic stroke. However, this causal association cannot be definitely ascertained, given the descriptive nature of our series. More research is needed to explore this possible causal association. Key Words: Cannabinoids—Ischemic stroke—Vasospasm.

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Cannabis-Related Myocardial Infarction and Cardioembolic Stroke

Dimitri Renard, MD, Guillaume Taieb, MD, Guillaume Gras-Combe, MD, and Pierre Labauge, MD, PhD

We report a 33-year-old man with a history of chronic cannabis use who sustained myocardial infarction followed by cerebral infarction after a recent significant increase in cannabis use. This is the first case of cannabis-associated stroke of probable cardioembolic origin. Key Words: Drugs—brain ischemia—cardiac ischemia.

© 2010 by National Stroke Association
Multiple Cerebral Infarcts in a Young Patient Associated With Marijuana Use

Volpon, Leila Costa MD; Sousa, Camila Lacerda Muniz de Melo MD; Moreira, Silvia Keiko Kavaguti MD; Teixeira, Sara Reis MD; Carlotti, Ana Paula de Carvalho Panzeri MD

Case Reports

Cerebrovascular events associated with marijuana use have been reported previously. This association is plausible, but not well-established yet. A 14-year-old girl, long-term heavy cannabis user, presented with generalized tonic-clonic seizures and decreased level of consciousness a few hours after smoking cannabis. Brain magnetic resonance imaging showed multiple areas of acute, subacute and chronic ischemic lesions in the left frontal lobe, basal ganglia, and corpus callosum. History of other illicit drug use and other known causes of stroke were ruled out. Cannabis might cause stroke through direct effects on the cerebral blood circulation, orthostatic hypotension, vasculitis, vasospasm, and atrial fibrillation. Long-term daily use of marijuana in young people may cause serious damage to the cerebrovascular system.
Cerebellar Infarction in Adolescent Males Associated With Acute Marijuana Use

Thomas Geller, MD†‡; Laura Loftis, MD‡; and David S. Brink, MD§

ABSTRACT. Objective. To demonstrate the clinical characteristics, radiologic findings, and neuropathological features of tetrahydrocannabinol-related posterior fossa ischemic stroke in adolescent patients.

Design. A retrospective case and chart review of 3 cases encountered at a tertiary care institution over a span of 5 years.

Setting. Inpatient and intensive care hospitalization units managing children and adolescents.

Subjects. Male adolescent patients with ischemic cerebellar stroke after use of marijuana.

Diagnostic Investigations. Computed tomography brain scans (3 subjects), magnetic resonance imaging brain study (1 subject), cerebral arteriography (1 subject), cerebellar biopsy (1 subject), and necropsy (2 subjects).

Results. Three adolescent males had similar presentations of headache, fluctuating level of consciousness or lethargy, visual disturbance, and variable ataxia after self-administration of marijuana. They developed primary cerebellar infarctions within days after the exposure that could not be attributed to supratentorial herniation syndromes and only minimally involved brainstem structures.

Marijuana and the Cardiovascular System

Cannabis-Associated Arterial Disease

Anne Claire Desbois,1,2 and Patrice Cacoub,1,2 Paris, France

Background: The aim of this study was to describe the different arterial complications reported in cannabis smokers.

Methods: This study was a literature review.

Results: Cannabis use was found to be associated with stroke, myocardial infarction, and lower limb arteritis. Arterial disease involved especially young men. There was a very strong temporal link between arterial complications and cannabis use for stroke and myocardial infarction episodes. Patient outcome was closely correlated with cannabis withdrawal and relapses associated with cannabis rechallenge. Cannabis use was associated with particular characteristics of arterial disease. The increased risk of myocardial infarction onset occurred within 1 hour of smoking marijuana compared with periods of non-use. Strokes occurred mainly in the posterior cerebral circulation. Compared with cohorts of thromboangiitis obliterans patients, those with cannabis-associated limb arteritis were younger, more often male, and had more frequent unilateral involvement of the lower limbs at clinical presentation.

Conclusion: Cannabis use is associated with arterial disease such as stroke, myocardial infarction, and limbs arteritis. It appears essential to investigate cannabis use in young patients presenting with such arterial manifestations, as outcome is closely correlated with cannabis withdrawal.
Marijuana and the Cardiovascular System

Cases Journal

Case Report

Ventricular fibrillation triggered by marijuana use in a patient with ischemic cardiomyopathy: a case report
Adrian Baranchuk*, Amer M Johri, Christopher S Simpson, Michelle Methot and Damian P Redfearn

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* Corresponding author

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Received: 11 September 2008
Accepted: 3 December 2008

Abstract

Background: A 60-year-old man presented to the emergency department with a left eye orbital rupture sustained during a fall due to syncope shortly after smoking more than his usual amount of marijuana.

Case presentation: The patient reported experiencing a shock from his implantable cardioverter-defibrillator (ICD) device prior to the loss of consciousness. There was no biochemical, electrocardiographic, or clinical evidence of ischemia. ICD interrogation revealed one episode of ventricular fibrillation which was appropriately sensed and treated with a single shock of 35 Joules.

Conclusion: Although the cardiovascular effects of marijuana are usually well tolerated in young healthy users, its use may trigger life-threatening arrhythmias in patients with structural heart disease. To the best of our knowledge, this is the first report on a case of ventricular fibrillation triggered by marijuana use in a patient with an ICD.

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Prolonged Atrial Fibrillation Precipitated by New-Onset Seizures and Marijuana Abuse

18-yr old male

We report a case of prolonged atrial fibrillation (AF) precipitated by new-onset generalized tonic-clonic convulsions and marijuana abuse in a developmentally normal 18-yr-old adolescent with a structurally normal heart. Our case highlights an interesting association and a unique pathophysiology between generalized tonic-clonic convulsions, marijuana abuse, and AF. We suggest that seizures and marijuana abuse should be considered in the differential diagnosis of the etiology of AF in children. Pediatrics 2014;133:e443–e446
Marijuana and the Cardiovascular System

Abstract 14100: Marijuana (Cannabis) Use is an Independent Predictor of Stress Cardiomyopathy in Younger Men
Amitoq Singh, Sahil Agrawal, Mark Feagley, Yugandhar Manda, Sudip Nanda, Jamshid Shirani

Circulation 2016;134A14100

Abstract

Background: Increased accessibility, recreational use and regional legalization of marijuana has been paralleled by widespread recognition of its serious cardiovascular complications (AMI, stroke, sudden death) particularly in the young. Cannabinoids have been implicated in pathogenesis of myocardial dysfunction through receptor and non-receptor mediated pathways. We aimed to examine trends in hospital admissions and outcomes of adults with transient ventricular regional ballooning (TVRB) in temporal relation to marijuana use.

Methods: Search of 2003-2011 Nationwide Inpatient Sample database identified 33,343 admissions for TRVB of which 210 (0.06%) were temporally related to active marijuana use. Demographics, clinical characteristics and outcomes of the two groups were compared.

Results: Marijuana users (MU) were younger (44±14-vs-66±13 years), more often male (36%-vs-8%), and had lower prevalence of hypertension (38%-vs-62%), diabetes (2.4%-vs-17.6%), and hyperlipidemia (15.7%-vs-52.4%) while more often suffered from depression (32.9%-vs-14.5%), psychosis (11.9%-vs-3.8%), anxiety disorder (28.4%-vs-16.2%), alcoholism (13.3%-vs-2.8%), tobacco use (73.3%-vs-28.6%) and poly-substance abuse (11.4%-vs-0.3%) [all p<0.001]. MU more often suffered cardiac arrest and required placement of an ICD while congestive heart failure was more frequently observed in non-marijuana users (NMU) [Table]. Multivariable binary regression analysis on entire database (n=71,753,000), adjusted for known risk factors for TVRB, identified marijuana use as an independent predictor of TVRB [OR=1.994 (95% CI=1.716-2.317), p<0.0001].

Conclusions: Marijuana use is linked to TVRB in a distinct cohort of younger individuals and is associated with significant morbidity despite younger age and more favorable cardiac risk factor profile compared to TVRB in NMU.
Marijuana and the Cardiovascular System

LETTER TO THE EDITOR

Reversible cardiomyopathy associated with acute inhaled marijuana use in a young adult

To the Editor:

Marijuana is the most frequently abused illicit drug globally (1, 2). It is rarely associated with cardiovascular events after acute administration (3, 4). Cardiac failure may result from chronic use (5). Marijuana’s pervasive use may lead to a significant burden of cardiovascular sequelae, which includes, with this report, the potential for toxic cardiomyopathy.

A 31-year-old woman presented to the Emergency Department with agitation (E = 4, V = 2, M = 5; GCS 11). She became confused after having smoked a large amount of marijuana. She was combative, with blood pressure 125/60 mm Hg, heart rate 110/min in sinus rhythm, respiratory rate 25/min; temperature 36.3°C. Both pupils were 1 mm and sluggish. Scleral injection was present. ...............

Conclusions:

Although cardiac dysfunction in this case cannot conclusively nor solely be attributed to marijuana, acute cardiomyopathy appeared to follow use of inhaled marijuana in a woman with no previous cardiovascular disease. This temporal association adds to the small body of literature on cardiovascular morbidity associated with marijuana.
Marijuana and the Cardiovascular System

Case Report

Sudden unexpected death under acute influence of cannabis

Benno Hartung a,∗, Silke Kauferstein b, Stefanie Ritz-Timme c, Thomas Daldrup a

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Cardiovascular events
Hypertensive crisis

ABSTRACT

The acute toxicity of cannabinoids is said to be low and there is little public awareness of the potentially hazardous cardiovascular effects of cannabis, e.g., marked increase in heart rate or supine blood pressure. We describe the cases of two young, passive healthy men who died unexpectedly under the acute influence of cannabinoids. To our knowledge, these are the first cases of suspected fatal cannabinoid intoxications where full postmortem investigations, including autopsy, toxicological, histological, immunohistochemical and genetical examinations, were carried out. The results of these examinations are presented. After exclusion of other causes of death we assume that the young men experienced fatal cardiovascular complications caused by smoking cannabis.

Case 1 23-yr old male

A 23-year-old male without known relevant illnesses suddenly collapsed while using public transport and died after 40 min of unsuccessful cardiopulmonary resuscitation with a clinical picture of ventricular fibrillation. A small amount of marijuana was found in his pockets.

Toxicological examinations proved the acute influence of cannabis (femoral blood: THC 5.2 ng/ml, 11-OH-THC 1.8 ng/ml, THC-COOH 12.9 ng/ml; brain tissue: THC 13.4 ng/g, 11-OH-THC 7.0 ng/g, THC-COOH 4.3 ng/g). Screening tests for other common drugs showed negative results.

As there is no known medical history and as both cardiac chambers showed normal thickness, we assume a dilatative cardiomyopathy as explanation for the hypertrophy of the cardiac walls.

Case 2 21-yr old male

A 21-year-old male with a history of substance abuse (alcohol, amphetamines and cocaine until about 2 years before death; occasionally cannabis) but without known cardiovascular diseases was found dead at home by his girlfriend. Next to the body an ashtray, rolling paper and a sealable plastic bag containing remnants of marijuana were found.

Toxicological examinations proved the acute influence of cannabis (femoral blood: THC 1.9 ng/ml, 11-OH-THC 0.8 ng/ml, THC-COOH 10.1 ng/ml; brain tissue: THC 6.3 ng/g, 11-OH-THC 2.3 ng/g, THC-COOH 2.3 ng/g). General unknown screening for other common drugs was negative with the exception of nicotine and caffeine levels.

We concluded that death occurred due to acute global cardiac failure under the acute influence of cannabis.
CASE REPORT

Pediatric Death Due to Myocarditis
After Exposure to Cannabis

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**University of Colorado School of Medicine at Anschutz Medical Center, Department of Emergency Medicine, Aurora, Colorado

Section Editor: Shadi Lahham, MD, MS
Submission history: Submitted November 29, 2016; Revision received January 20, 2017; Accepted January 21, 2017
Electronically published: March 16, 2017
Full text available through open access at http://escholarship.org/uc/item3mpcm
DOI: 10.5811/opcom.2017.1.33249

Since marijuana legalization, pediatric exposures to cannabis have increased. To date, pediatric deaths from cannabis exposure have not been reported. The authors report an 11-month-old male who, following cannabis exposure, presented with central nervous system depression after seizure, and progressed to cardiac arrest and died. Myocarditis was diagnosed post-mortem and cannabis exposure was confirmed. Given the temporal relationship of these two rare occurrences – cannabis exposure and sudden death secondary to myocarditis in an 11-month-old – as well as histological consistency with drug-induced myocarditis without confirmed alternate causes, and prior reported cases of cannabis-associated myocarditis, a possible relationship exists between cannabis exposure in this child and myocarditis leading to death. In areas where marijuana is commercially available or decriminalized, the authors urge clinicians to preventively counsel parents and to include cannabis exposure in the differential diagnosis of patients presenting with myocarditis. [Clin Pract Cases Emerg Med. 2017;1(3):166–170.]

Glasgow coma scale of 4
Marijuana and the Cardiovascular System

Glasgow coma scale of 15

Practice

Cases

Hypotension associated with ingestion of cannabinoids in two children with cancer

Amanda M. Li MD MSc, S. Rod Raschuk MD MHS

Case 1  BP = 50/30

A two-year-old boy with an epidermoidoma was admitted for administration of chemotherapy (cyclophosphamide, methotrexate, etoposide and cisplatin). Previous cycles of the same chemotherapy had been well tolerated, with no hypotension. Independent of medical advice, the patient’s parents had been giving him [tetrahydrocannabinol (THC) and cannabidiol (CBD)] oil drops orally. Five days after his last chemotherapy dose, the patient was noted to be lethargic through the day, with downsloping blood pressure readings.

The patient’s blood pressure dropped to 50/30 mm Hg during deep sleep, and his skin appeared mottled, with delayed capillary refill. His heart rate was not substantially elevated, at 107 beats/min; his temperature, respiration rate and oxygen saturation levels were normal. Upon being moved, the child was unresponsive, with normal findings on neurologic and cardiorespiratory examination. He had maintained good urine output and did not have clinical signs suggestive of dehydration.

The patient’s mother then reported that the family had independently increased the number of THC:CBD oil drops over the preceding few days from one drop three times daily to three drops three times daily. The last dose had been given 10-15 hours before the nadir in blood pressure.

The patient was given a rapid 20-mL/kg bolus of normal saline and maintenance fluid support, which corrected the hypotension. Empiric antibiotic therapy was started, although blood culture results were subsequently negative. The patient’s blood pressure remained normal, even during subsequent periods of fever and sepsis.

Case 2  BP = 80/33

A four-year-old girl at very high risk of acute lymphoblastic leukemia was admitted for a bone marrow transplant. By day 30, she had full engraftment of transplanted marrow. During this period, she received treatment for suspected fungal lesions of her spleen but did not have fungemia.

Despite frequent episodes of intercurrent fever, the patient was never hypotensive.

On day 30, the patient’s mother administered a few drops of THC:CBD oil of unknown concentration to see if it would help alleviate symptoms of discomfort and pain. Nine hours later, while the patient was asleep, her diastolic blood pressure dropped from a baseline of 47 mm Hg to 33 mm Hg, and her systolic pressure dropped from 89 mm Hg to 80 mm Hg. She was febrile at 38.6°C and had a pulse of 120 beats/min. Over the preceding two days, the patient had been persistently febrile with normal blood pressure readings. She had been given empiric antibiotic and antifungal therapy, but blood culture results remained negative.

The patient was febrile but alert and had a Glasgow Coma Scale score of 15. Her distal pulses were palpable but not bounding, and she did not appear clinically dehydrated.

The patient was given a rapid 20-mL/kg bolus of normal saline and extra maintenance intravenous fluid, and her blood pressure returned to normal. No further THC:CBD oil drops were administered, and she had no further episodes of hypotension.
A single dose of cannabidiol reduces blood pressure in healthy volunteers in a randomized crossover study

Khalid A. Jadoon, Garry D. Tan, and Saolise E. O'Sullivan

Background. Cannabidiol (CBD) is a nonpsychoactive phytocannabinoid used in multiple sclerosis and intractable epilepsies. Preclinical studies show CBD has numerous cardiovascular benefits, including a reduced blood pressure (BP) response to stress. The aim of this study was to investigate if CBD reduces BP in humans.

Methods. Nine healthy male volunteers were given 600 mg of CBD or placebo in a randomized, placebo-controlled, double-blind, crossover study. Cardiovascular parameters were monitored using a finometer and laser Doppler.

Results. CBD reduced resting systolic BP (-6 mmHg; P < 0.05) and stroke volume (-8 ml; P < 0.05), with increased heart rate (HR) and maintained cardiac output. Subjects who had taken CBD had lower BP (-5 mmHg; P < 0.05, especially before and after stress), increased HR (+10 bpm; P < 0.01), decreased stroke volume (-13 ml; P < 0.01), and a blunted forearm skin blood flow response to isometric exercise. In response to cold stress, subjects who had taken CBD had blunted BP (-6 mmHg; P < 0.01) and increased HR (+7 bpm; P < 0.05), with lower total peripheral resistance.

Conclusions. This data shows that acute administration of CBD reduces resting BP and the BP increase to stress in humans, associated with increased HR. These hemodynamic changes should be considered for people taking CBD. Further research is required to establish whether CBD has a role in the treatment of cardiovascular disorders.
Marijuana and the Cardiovascular System: the role for non-traditional cannabinoid receptors

Activation of GPR18 with cannabidiol causes hypotension (low blood pressure)
Marijuana and Fetal Development

The Medical Cannabis Law in Maryland, as it pertains to providers who treat pregnant women

LAWRENCE J. HOGAN, JR., Governor Ch. 474
Chapter 474
(House Bill 104)
AN ACT concerning
Medical Cannabis – Written Certifications – Certifying Providers
FOR the purpose of authorizing certain dentists, podiatrists, nurse midwives, and nurse practitioners, in addition to physicians, to issue written certifications to qualifying patients by substituting the defined term “certifying provider” for “certifying physician” as it relates to laws governing medical cannabis; making conforming changes; making a stylistic change; providing for a delayed effective date; and generally relating to providers authorized to provide written certifications for medical cannabis.
Approved by the Governor, May 10, 2016.
ACOG COMMITTEE OPINION

Recommendations

• 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.
Yet, the NACPM association for nurse midwives has no official position on marijuana
And the American College of Nurse-midwives also has yet to issue a formal position on marijuana use during pregnancy.
AHA Scientific Statement

Marijuana and Fetal Development

Noninherited Risk Factors and Congenital Cardiovascular Defects: Current Knowledge
A Scientific Statement From the American Heart Association Council on Cardiovascular Disease in the Young
Endorsed by the American Academy of Pediatrics

Kathy J. Jenkins, MD, MPH, FAHA; Adolfo Correa, MD, MPH, PhD, FACE; Jeffrey A. Feinstein, MD, MPH; Lorenzo Botto, MD; Amy E. Britt, MS, FAHA; Stephen R. Daniels, MD, PhD, FAHA; Martha Elikson, RN, MS, FAHA; Carole A. Wames, MD; Catherine L. Webb, MD. MS, FAHA

Circulation. 2007;115:2995-3014; originally published online May 22, 2007;

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<td></td>
<td>Pulmonary stenosis</td>
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<tr>
<td></td>
<td>d-TGA with intact ventricular septum</td>
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<td>Tetralogy of Fall</td>
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<td>TAPVR</td>
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<td>AVSD, nonchromosomal</td>
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<td>Caudal's anomaly</td>
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<td>ASD, 21, 23</td>
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<td>VSD</td>
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VLDL indicates phenylethanolamines; d-TGA, d-transposed transposition of the great arteries; AVSD, atrioventricular septal defect; HLHS, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; SD, birth weight; NOS, nontherapeutic nonsteroidal antiinflammatory drugs; TAPVR, total anomalous pulmonary venous return.

Characteristics of the coarctation or neonatal echocardiogram if any of these exposures are present based on the type and type of exposure and the timing of the exposure in gestation.

*If not available.

Often reduces if mother took folic acid simultaneously.

If both parents smoked.
"There is substantial evidence of a statistical association between maternal cannabis smoking and lower birth weight of the offspring". This conclusion was based on a substantial number of well-controlled studies.

**Human Studies**

**Leemaqz SY et al.** *Maternal marijuana use has independent effects on risk for spontaneous preterm birth but not other common late pregnancy complications*. Reprod Toxicol. 2016;62:77-86.

**Spontaneous preterm birth**: “When adjusted for maternal age, cigarette smoking, alcohol and SEI (socioeconomic index), continued marijuana use had a greater effect size, OR (Odds Ratio) of 5.44.” This study was relatively small (236 pre-term births out of 5588 total births) and though well-controlled, should be repeated.
Animal studies

Benevenuto SG et al., *Recreational use of marijuana during pregnancy and negative gestational and fetal outcomes: An experimental study in mice.* Toxicology. 2017 Feb 1;376:94-101

"Five minutes of daily (low dose) exposure during pregnancy resulted in reduced birthweight.....females from the Cannabis group presented reduced maternal net body weight gain, despite a slight increase in their daily food intake compared to the control group.“ This animal study confirmed prior human results.


“Data from various animal models suggests that *in utero* exposure to cannabinoids results in profound T cell dysfunction and a greatly reduced immune response to viral antigens.” No human data have been collected on this topic.
**Human study**, postnatal MRI of brain


"+MJ (marijuana-exposed) neonates had hypo-connectivity in all clusters compared with –MJ (marijuana unexposed) and CTR (control) groups. Altered striatal connectivity to areas involved in visual spatial and motor learning, attention, and in fine-tuning of motor outputs involved in movement and language production may contribute to neurobehavioral deficits reported in this at-risk group. Disrupted anterior insula connectivity may contribute to altered integration of interoceptive signals with salience estimates, motivation, decision-making, and later drug use.” This study involved MRI scans while the infants were asleep at 2-6 weeks after birth and included 20 marijuana-exposed infants (with or without co-exposure to alcohol, nicotine, antidepressants, opiates); 23 infants exposed to alcohol, nicotine, antidepressants or opiates; and 20 drug-free controls. The methods to separate out the marijuana-specific effects were complex and the results should be confirmed by future research.

**Animal study**, postnatal molecular profiling of endocannabinoid system


"Here, we show that repeated THC exposure disrupts endocannabinoid signaling, particularly the temporal dynamics of CB1 cannabinoid receptor, to rewire the fetal cortical circuitry....these data highlight the maintenance of cytoskeletal dynamics as a molecular target for cannabis.....Our mRNA and protein profiling of molecular components controlling 2-AG (endocannabinoid) metabolism suggest that THC not only can act as a "functional antagonist (i.e. displacement of endocannabinoid binding to the CB1R (receptor), but can disrupt 2-AG signaling by reducing both CB1R and DAGL-alpha expression during cortical development"

**Review of human studies:** “These studies showed that the consequences of prenatal exposure to cannabis are rather subtle. Immediately after birth, there is little evidence for a prenatal cannabis effect either upon growth or behavior. However, **beyond the age of 3, there are findings suggesting an association between prenatal cannabis exposure and aspects of cognitive behavior that fall in the domain of executive functions.** Executive functions refer to higher-order cognitive functions such as cognitive flexibility, sustained and focused attention, planning and working memory. These functions enable us to organize and manage the many tasks in our daily life.”

**Review of animal studies:** “Prenatal exposure to a moderate dose of the synthetic CB1 cannabinoid receptor agonist WIN55,212-2 (0.5 mg/kg from GD 5 to GD 20) has been shown to induce a disruption of memory retention in 40- and 80-day-old rat offspring tested in the inhibitory avoidance task...Morphological experiments have shown that prenatal exposure to WIN55,212-2 also affects neuronal proliferation: a different neurite growth pattern was observed in cortical cell cultures obtained from pups born from mothers exposed to WIN55,212-2 during pregnancy...abnormal neurite outgrowth, characterized by impairments of neurite branching..... In addition, prenatal exposure to WIN55,212-2 has been found to induce long-term changes in the activity of the endocannabinoid system: in particular, the functionality of CB1 receptors in the hippocampus differed between adult WIN55,212-2- and vehicle-exposed offspring...... the dose of WIN55,212-2 used in the studies described above corresponds to a moderate, or even to a low, exposure to cannabis in humans....... **THC, administered during the perinatal period at a dose that is not associated with gross malformations and/or overt signs of toxicity, induces cognitive impairments in the adult offspring.**”
**Human studies**


“PME (Prenatal Marijuana Exposure) in the first and third trimesters predicted **significantly increased levels of depressive symptoms**. This finding remained significant after controlling for all identified covariates from both the prenatal period and the current phase at age 10.


“Marijuana exposure during gestation **marginally predicted depression/anxiety at age 10.**”


“Sixteen participants were prenatally exposed to marijuana while 15 had no prenatal marijuana exposure...**consistently increased left posterior brain activity in the prenatally exposed group** compared with the control group.”

**Marijuana and Fetal Development**
More pregnant women are using…
Cannabinoid Hyperemesis Syndrome: A Cause of Refractory Nausea and Vomiting in Pregnancy

Altmir, Veronica I, MD, MPH, Liss, Jill MD, Metz, Tori D, MD, MS, Blackhart, Elaine MD

Obstetrics & Gynecology: June 2016 - Volume 125 - Issue 6 - p 1484-1486
doi: 10.1097/AOG.0000000000000595
Contents: Case Report

BACKGROUND: Cannabinoid hyperemesis syndrome is a condition present among chronic cannabis users resulting in abdominal pain, intractable nausea and vomiting, and compulsive bathing behaviors. Given the recent legalization of marijuana in certain areas of the United States, the incidence of this condition may increase among pregnant women.

CASE: We report the case of a pregnant 26-year-old woman with multiple admissions for episodic nausea and vomiting resulting in Mallory-Weiss esophageal tears, dehydration, and abdominal pain who was noted to be showering compulsively during her hospitalizations. After an extensive workup for the etiology of her intractable nausea and pain, she was diagnosed with cannabinoid hyperemesis syndrome, which is treated simply with abstinence from marijuana use.

CONCLUSION: Cannabinoid hyperemesis syndrome should be considered in pregnant women with intractable nausea relieved by frequent hot bathing. If considering this diagnosis, extensive diagnostic testing can be avoided and the correct therapy, abstinence from cannabis use, can be recommended.
Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment—a Systematic Review

Abstract

Cannabinoid hyperemesis syndrome (CHS) is a syndrome of cyclic vomiting associated with cannabis use. Our objective is to summarize the available evidence on CHS diagnosis, pathophysiology, and treatment. We performed a systematic review using MEDLINE, Ovid MEDLINE, Embase, Web of Science, and the Cochrane Library from January 2000 through September 24, 2015. Articles eligible for inclusion were evaluated using the Grading and Recommendations Assessment, Development, and Evaluation (GRADE) criteria. Data were abstracted from the articles and case reports and were combined in a cumulative synthesis. The frequency of identified diagnostic characteristics was calculated from the cumulative synthesis and evidence for pathophysiologic hypothesis as well as treatment options were evaluated using the GRADE criteria. The systematic search returned 2798 articles. After duplicates were removed, 1255 abstracts were reviewed and 483 were included. Fourteen diagnostic characteristics were identified, and the frequency of these characteristics was as follows: history of regular cannabis for any duration of time (100%), cyclic nausea and vomiting (100%), resolution of symptoms after stopping cannabis (96.4%), compulsive hot baths with symptom relief (92.3%), male predominance (70.9%), abdominal pain (85.1%), and at least weekly cannabis use (97.4%). The pathophysiology of CHS remains unclear with a dearth of research dedicated to investigating its underlying mechanism. Supportive care with intravenous fluids, dopamine antagonists, topical capsaicin cream, and avoidance of narcotic medications has shown some benefit in the acute setting. Cannabis cessation appears to be the best treatment. CHS is a cyclic vomiting syndrome, preceded by daily to weekly cannabis use, usually accompanied by symptom improvement with hot bathing, and resolution with cessation of cannabis. The pathophysiology underlying CHS is unclear.
Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study

Marta Di Forti, Arianna Marconi, Elena Carra, Sara Fraietta, Antonella Trotta, Matteo Bonomo, Francesca Bianconi, Poonam Gardner-Sood, Jennifer O’Connor, Manuela Russo, Simona A Stilo, Tiago Reis Marques, Valeria Mondelli, Paola Dazzan, Carmine Pariante, Anthony S David, Fiona Gaughran, Zerrin Atakan, Conrad Iyegbe, John Powell, Craig Morgan, Michael Lynskey, Robin M Murray

Summary

Background The risk of individuals having adverse effects from drug use (eg, alcohol) generally depends on the frequency of use and potency of the drug used. We aimed to investigate how frequent use of skunk-like (high-potency) cannabis in south London affected the association between cannabis and psychotic disorders.

Findings Between May 1, 2005, and May 31, 2011, we obtained data from 410 patients with first-episode psychosis and 370 population controls. The risk of individuals having a psychotic disorder showed a roughly three-times increase in users of skunk-like cannabis compared with those who never used cannabis (adjusted odds ratio [OR] 2.92, 95% CI 1.52–3.45, p=0.001). Use of skunk-like cannabis every day conferred the highest risk of psychotic disorders compared with no use of cannabis (adjusted OR 5.4, 95% CI 2.81–11.31, p=0.002). The population attributable fraction of first-episode psychosis for skunk use for our geographical area was 24% (95% CI 17–31), possibly because of the high prevalence of use of high-potency cannabis (218 [53%] of 410 patients) in our study.
Dose-response studies: the more frequent the use and the more concentrated the product, the more likely a psychotic outcome?

Yes


“Cannabis was associated with an increased risk of developing schizophrenia in a dose dependent fashion.....for subjects who had ever used cannabis ...adjusted odds ratio 1.1 to 1.5...... The adjusted odds ratio for (developing schizophrenia from) using cannabis >50 times was 6.7” In common with subsequent studies, adjustment made for many variables, including the following specific to this study: psychiatric diagnoses at conscription, IQ score, personality variables concerned with interpersonal relationships, place of upbringing, paternal age, and cigarette smoking; disturbed behavior in childhood, history of alcohol misuse, family history of psychiatric illness, poor social integration, financial situation of the family and father's occupation. All variables used for adjustment should be chosen with care to exclude factors which are unrelated to outcome based on strong theoretical considerations or research data. Factors unrelated to outcome introduce noise into the analysis and reduce analytical power.

Yes


“Cannabis any use at baseline and cumulative frequency were associated with a high risk of psychosis outcome” Table 2: Lowest level (use 3 days per month or less): adjusted OR (odds ratio) of 1.23........Mid level (use 1 to 4 days per week): adjusted OR of 4.9......Highest level (use from 4 days per week to every day): adjusted OR of 6.81
Ruling out self-medication: Does the marijuana use generally come before the psychosis?

Yes


“cannabis use is associated with an increased risk of experiencing schizophrenia symptoms, even after psychotic symptoms preceding the onset of cannabis use are controlled for, indicating that cannabis use is not secondary to a preexisting psychosis”

Yes


"Any cannabis use at baseline increased the risk of psychotic symptoms according to the M-CIDI at follow up four years later in a dose-response fashion..... Predisposition for psychosis at baseline did not significantly predict cannabis use at follow up four years later....the data did not support the self medication hypothesis".
Ruling out self-medication: Does the marijuana use generally come before the psychosis?.... (continued)

Yes


“incident cannabis use over the period from baseline to T2 (timepoint-2) increased the risk of later incident psychotic symptoms over the period from T2 to T3 (adjusted odds ratio 1.9)..... There was *no evidence for self medication effects*, as psychotic experiences at T2 did not predict incident cannabis use between T2 and T3 (adjusted odds ratio 0.8)”

Yes and No


cannabis use at age 16 predicted psychosis vulnerability at age 19...Furthermore, psychosis vulnerability at ages 13 and 16 predicted cannabis use at, respectively, ages 16 and 19. Conclusions: **Cannabis use predicts psychosis vulnerability in adolescents and vice versa**, which suggests that there is a bidirectional causal association between the two.** Studies that are outliers should be checked for methodological differences with the prior work:** this study is criticized because the subjects graded themselves on psychosis vulnerability on a multiple choice type test, rather than a clinician’s rating of them through an interview:** Lewis G, Heron J, Zammit S. Commentary on Griffith-Lendering et al. (2013): cross-lagging cannabis and psychosis vulnerability. Addiction. 2013; 108(4):741-2. **Subjects (particularly adolescents) often overrate their psychotic experiences in questionnaires, particularly in regards to paranoia.**
Is marijuana use associated with an earlier age of onset in those who develop schizophrenia?

Yes


“The results of meta-analysis provide evidence for a relationship between cannabis use and earlier onset of psychotic illness, and they support the hypothesis that cannabis use plays a causal role in the development of psychosis in some patients.”

Yes


“Our results suggest that cannabis use is associated with a reduction in age at onset in both schizophrenic and bipolar patients.”
Are those with a familial risk for schizophrenia more likely to use marijuana?

No


“Cannabis use predicted schizophrenia [adjusted odds ratio (OR) cases compared to general hospital controls 7.8, 95% confidence interval (CI) 2.7-22.6; adjusted OR cases compared to siblings 15.9 (95% CI 1.5-167.1)], but genetic predisposition for schizophrenia did not predict cannabis use.”
Do studies comparing siblings show greater risk in the sibling using marijuana?

By comparing siblings, helps to control for a host of genetic and environmental factors

Yes


“Compared with those who had never used cannabis, young adults who had 6 or more years since first use of cannabis (i.e., who commenced use when around 15 years or younger) were twice as likely to develop a nonaffective psychosis......This study provides further support for the hypothesis that early cannabis use is a risk-modifying factor for psychosis-related outcomes in young adults. The use of sibling pairs reduces the likelihood that unmeasured confounding explains these findings.”

Yes


“Allowing 7 years from initial CA (cannabis abuse) registration to later diagnosis, the risk for schizophrenia in discordant full sibling pairs remained almost twofold....The results of this study therefore lend support to the etiologic hypothesis, that CA (cannabis abuse) is one direct cause of later schizophrenia.”
If the active ingredient of marijuana is administered in the clinic, can psychotic symptoms be measured?

Yes


“Δ-9-THC (1) produced schizophrenia-like positive and negative symptoms; (2) altered perception; (3) increased anxiety; (4) produced euphoria; (5) disrupted immediate and delayed word recall, sparing recognition recall; (6) impaired performance on tests of distractibility, verbal fluency, and working memory..... These data indicate that D-9-THC produces a broad range of transient symptoms, behaviors, and cognitive deficits in healthy individuals that resemble some aspects of endogenous psychoses.” The subjects were screened to exclude anyone with a history of a major mental illness or substance abuse disorder or anyone with a family history of a major mental disorder.

Yes


“THC significantly increased paranoia, negative affect (anxiety, worry, depression, negative thoughts about the self), and a range of anomalous experiences, and reduced working memory capacity.” Note that all subjects were required (by ethical guidelines) to have prior marijuana use experience.
If the active ingredient of marijuana is administered in the clinic, can psychotic symptoms be measured? (continued)

Yes


“Exclusion criteria included: current pregnancy, a history of mental illness, drug or alcohol dependence (excluding nicotine), current or past severe medical disorders, or a history of major mental illness in a first-degree family member.....**Compared with placebo, THC evoked positive and negative psychotic symptoms,** as measured by the positive and negative syndrome scale (p<0.001)” Results: **40% of participants showed increases in PANSS positive symptom scores of >4 points.** Note that all subjects were required (by ethical guidelines) to have prior marijuana use experience.

Yes


“Pairwise comparisons revealed that **9-THC significantly increased the severity of psychotic symptoms compared with placebo** (P<.001) and CBD (P<.001).” Again, approximately **40% of participants showed increases in PANSS positive psychotic symptom scores** (Figure 2). Note that all subjects were required (by ethical guidelines) to have prior marijuana use experience.
One gene identified which could mediate marijuana-induced psychosis (in subjects with no family history of schizophrenia)

Morgan CJ, Freeman TP, Powell J, Curran HV. **AKT1 genotype moderates the acute psychotomimetic effects of naturally smoked cannabis in young cannabis smokers.** Transl Psychiatry. 2016;6:e738.

"Although previous studies have suggested that the acute effects of cannabis are mediated by the AKT1 polymorphism, they have not assessed acute effects at the time of smoking cannabis and relied instead on retrospective reports. Further, previous studies were all of patients either with psychotic disorders or at a familial risk. The current study, therefore, set out to examine the gene x cannabis use interaction in a group of healthy young cannabis users, with no family history of schizophrenia, assessed both at the time of smoking cannabis and when non-intoxicated. Variation at the rs2494732 locus of the AKT1 gene predicted acute psychotic response to cannabis, along with dependence on the drug and baseline schizotypal symptoms.** Note that all subjects were required (by ethical guidelines) to have prior marijuana use experience and the presence of schizotypal symptoms in a subset of those subjects, may therefore have been associated with their marijuana use.
Is the conversion rate from temporary, drug-induced psychotic breaks to chronic psychosis higher for marijuana than for other recreational drugs?

Yes


“Eight-year cumulative risk to receive a schizophrenia spectrum diagnosis was 46% for persons with a diagnosis of cannabis-induced psychosis ..... chances for amphetamine-, hallucinogen-, opioid-, sedative- and alcohol-induced (schizophrenia spectrum diagnoses) were 30%, 24%, 21%, and 5% respectively.”

Yes


“the highest risk of developing schizophrenia was found among cannabis users.” They compared alcohol, amphetamine, cannabis, cocaine, hallucinogens, opioids, sedatives and “other” (polydrug use or unknown).
Course of recovery from a psychotic break takes a while (even in the users who quit)


Recovery of global functioning at 8-years **best in those who quit using cannabis** (green line), but recovery still slow

---

**Fig. 1.** Global Assessment of Functioning (GAF) Outcome by Cannabis Use Group.
After a marijuana-induced psychotic break occurs, does it make a difference for recovery if you have a family history of schizophrenia?

"a high percentage of patients develop schizophrenia spectrum disorder after the cannabis-induced psychosis and the timing and rate of this outcome are independent of family history of psychiatric disorder"

No

About 50% of those with, and 50% of those without, a family history end up at the same point 9 years out, with a diagnosis of schizophrenia

Arch Gen Psychiatry. 2008;65(11):1269-1274

Familial Predisposition for Psychiatric Disorder

Comparison of Subjects Treated for Cannabis-Induced Psychosis and Schizophrenia

Mikkel Arendt, MScPsych, PhD; Preben B. Mortensen, DrMedSc; Raben Rosenberg, DrMedSc; Carsten B. Pedersen, MSc; Berit L. Waltoft, MSc
Summary of findings supporting a role for marijuana being causal for chronic psychosis

- Marijuana use increases the risk of a psychotic outcome in dose-responsive manner, based on usage frequency and strength of the product; high THC-strength strains increase the risk 5-fold with weekly use.

- The evidence for marijuana use preceding psychosis is strong, but is weak for psychosis leading to marijuana use. Furthermore, those with a family history of schizophrenia are no more likely to begin marijuana use than those without such a history.

- Marijuana use is associated with an earlier age of onset in those who develop schizophrenia.

- Administration of pure THC under controlled conditions in the clinic causes psychotic symptoms in fully 40% of individuals who have no family history of psychotic disorders; the genes controlling this effect have not been fully identified but one has been proposed to account for a portion of cases: AKT1.

- In studies of siblings, the sibling who uses marijuana is significantly more likely to develop chronic psychosis than the sibling who does not use; thereby controlling for genetic factors and many environmental factors.

- Marijuana leads the pack for rate of conversion from temporary drug-induced psychosis to chronic psychosis and that conversion is independent of family history; about 50% will transition.

- For the 50% who can recover from a marijuana-induced psychotic break, the recovery is not immediate following marijuana cessation, taking months to years; recovery doesn’t depend on family history; and if the subjects continue to use marijuana, their chances of recovery are very poor.
Acute suicidal urges and suicide

USA TODAY/Suffolk Poll: Despite economic optimism, Americans worry about Trump and the future  
Read

Young man leaps to death after eating pot-laced cookie

Sade Gurman, Associated Press  
Published 5:10 p.m. ET April 2, 2019 | Updated 3:30 p.m. ET April 2, 2019

An autopsy report lists marijuana intoxication as a significant contributing factor in the death of 15-year-old Levi Thamba Pong, a native of the Republic of Congo, who fell from a motel balcony on March 11.

Pong’s friends told investigators he ate the cookie and exhibited hostile behavior that included pulling things off walls and spitting eructingly, the report said.

Attempts by the three friends to calm Pong seemed to work until he went outside and jumped out of the balcony railing, according to the report.

Official at Northwest College in Powell, Wyo., says Pong started taking classes as an exchange student in January. He was studying engineering.

“The Northwest College campus community continues to grieve after Levi’s death,” the college said in a statement. “All of us were deeply saddened by this tragic, violent and fatal for his family.”

The medical examiner’s office had forensic tests done for at least 250 different substances, including bath salts and synthetic marijuana, which are known to cause strange behavior, the report said.

The poison control center in Coeur d’Alene, Idaho, received 74 calls for marijuana-related poisoning in 2015, according to the report.

Morbidity and Mortality Weekly Report (MMWR)

Notes from the Field: Death Following Ingestion of an Edible Marijuana Product — Colorado, March 2014

Weekly
July 24, 2015 / 64(28):771-772

Jessica B. Hancock-Allen, MSN1,2; Lisa Barker2; Michael VanDyke, PhD2; Dawn B. Holmes, MD2 (Author affiliations at end of text)

In March 2014, the Colorado Department of Public Health and Environment (CDPHE) learned of the death of a man aged 19 years after consuming an edible marijuana product. CDPHE reviewed autopsy and police reports to assess factors associated with his death and to guide prevention efforts. The decedent’s friends, aged 23 years, had purchased marijuana cookies and provided one to the decedent. A police report indicated that initially the decedent ate only a single piece of his cookie, as directed by the sales clerk. Approximately 30–60 minutes later, not feeling any effects, he consumed the remainder of the cookie.

During the next 2 hours, he reportedly exhibited grizzly speech and hostile behaviors. Approximately 3.5 hours after initial ingestion, and 2.5 hours after consuming the remainder of the cookie, he jumped off a fourth-floor balcony and died from trauma. The autopsy, performed 29 hours after time of death, found marijuana intoxication as a chief contributing factor. Quantitative toxicologic analyses for drugs of abuse, synthetic cannabinoids, and cathinones (“bath salts”) were performed on chest cavity blood by gas chromatography and mass spectrometry. The only confirmed findings were cannabinoids (7.2 ng/mL delta-9-tetrahydrocannabinol [THC] and 49 ng/mL delta-9 carboxy-THC, an inactive marijuana metabolite). The legal blood alcohol limit of 0.08% THC for driving a vehicle in Colorado is 5.0 ng/mL. This was the first reported death in Colorado linked to marijuana consumption without evidence of polysubstance use since the state approved recreational use of marijuana in 2012.
Acute suicidal urges and suicide

College graduate, 23, dies on Colorado ski vacation after eating four marijuana candies and THC-laced cookie and then shooting himself in the head

- Luke Goodman brought $28 worth of edibles and marijuana with his cousin on Saturday and the two went back to their condo in Keystone to get high.
- When the effects of the edibles didn’t immediately kick in after taking two, Goodman ate two more and a THC cookie - five times the recommended dosage.
- A few hours later, the college grad became withdrawn and started mumbling incoherently.
- Apparently unaware of his serious condition, his cousin went outside to use the hot tub and that’s when Goodman shot himself in the head.
- Goodman shot himself with his personal gun he brought on the vacation.
- Goodman’s family blame the tragedy on the edibles, since he had never appeared depressed or suicidal before taking the drugs.

By ASHLEY CULLER FOR DAILYMAIL.COM
PUBLISHED: 11:02 GMT, 29 March 2016 | UPDATED: 11:01 GMT, 29 March 2016

A popular college graduate died this past weekend in Colorado, after his family say he took too many marijuana candies and killed himself.

Luke Goodman, 23, of Tulsa, Oklahoma ate four times the prescribed amount of a peach tent marijuana edible candy. In addition to a THC-laced red velvet cookie and proceeded to shoot himself in the head with a gun he brought on the trip for protection.

Goodman’s family say he was a charismatic and outgoing young man who never showed signs of depression or suicidal thoughts before. They blame his death solely on the edibles.

It was 100% per cent the drugs. It was completely because of the drugs. It had consumed so much of him,” his mother Kim Goodman told KBS Denver.

Goodman was on a two-week ski trip with his family and friends when his parents dropped him off at the bus stop Saturday to go snowboarding with his cousin, Caleb Kowal.

Goodman’s parents were on their way back to Tulsa, and their son was going to spend the rest of the trip with his cousin.
Don’t Harsh Our Mellow, Dude

Maureen Dowd  JUNE 3, 2014

The caramel-chocolate flavored candy bar looked so innocent, like the Sky Bars I used to love as a child.

Sitting in my hotel room in Denver, I nibbled off the end and then, when nothing happened, nibbled some more. I figured if I was reporting on the social revolution rocking Colorado in January, the giddy culmination of pot Prohibition, I should try a taste of legal, edible pot from a local shop.

What could go wrong with a bite or two?

Everything, as it turned out.

Not at first. For an hour, I felt nothing. I figured I’d order dinner from room service and return to my more mundane drugs of choice, chardonnay and mediocre-movies-on-demand.

But then I felt a scary shudder go through my body and brain. I barely made it from the desk to the bed, where I lay curled up in a hallucinatory state for the next eight hours. I was thirsty but couldn’t move to get water. Or even turn off the lights. I was panting and paranoid, sure that when the room-service waiter knocked and I didn’t answer, he’d call the police and have me arrested for being unable to handle my candy.

I strained to remember where I was or even what I was wearing, touching my green corduroy jeans and staring at the exposed-brick wall. As my paranoia deepened, I became convinced that I had died and no one was telling me.

It took all night before it began to wear off, distressingly slowly. The next day, a medical consultant at an edibles plant where I was conducting an interview mentioned that candy bars like that are supposed to be cut into 16 pieces for novices; but that recommendation hadn’t been on the label.

In March, a 19-year-old Wyoming college student jumped off a Denver hotel balcony after eating a pot cookie with 65 milligrams of THC. In April, a Denver man ate pot-infused Karma Kandy and began talking like it was the end of the world, scaring his wife and three kids. Then he retrieved a handgun from a safe and killed his wife while she was on the phone with an emergency dispatcher.

“The whole industry was set up for people who smoked frequently. It needs to learn how to educate new users in the market. We have to create a culture of responsibility around edibles, so people know what to expect to feel,” said Andrew Freedman, the state’s director of marijuana coordination.
Marijuana use and **acute** suicide risk?

**Yes**


**Review**: “Among patients treated with cannabinoids, the following symptoms appeared in at least 2 studies: nausea, increased weakness, behavioral or mood changes (or both), **suicidal ideation or hallucinations (or both)**, dizziness or vasovagal symptoms (or both), fatigue, feelings of intoxication.”

**Yes**


**Case**: “he had smoked cannabis a few hours before. Soon after, he had experienced hopelessness and **impulse to commit suicide by fall**. ...He reported no stressful life event and was astonished by his suicidal thinking....None of his relatives had suffered from psychiatric disorder, substance of alcohol abuse.....The patient reported a similar episode of suicidal thought occurred three years before, just after smoking cannabis and spontaneously remitted.....Urine toxic screening text revealed the presence of cannabis and no trace of amphetamine, cocaine, opioids, barbiturates, or alcohol......The day after, the patient was free of symptoms and was discharged without therapy.”

**Yes**


**Case**: "we describe a case of a woman affected by MS and treated with baclofen and methylprednisolone, who developed important behavior changes, including **suicidal ideation, after 4 weeks of Sativex administration**.”

**Yes**


**Small clinical trial**: **One out of fourteen subjects** treated with dronabinol (prior to the treatment with the THC antagonist) reported **suicidal thoughts**: "one subject retrospectively reported 30 minutes of depressed mood, suicidal thoughts and paranoia"
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<td>Yes</td>
<td>&quot;Adolescent mood disorder and adolescent cannabis use both independently increased the odds of a suicide attempt 7-fold&quot;</td>
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<td>Yes</td>
<td>&quot;After covariate adjustment, compared with individuals who had never used cannabis, those who were daily users before age 17 years .. the odds of........ suicide attempt (6.83-fold)&quot;</td>
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<td>Yes</td>
<td>“The aim of the study was to determine excess mortality associated with cannabis use disorders...For different causes of death the SMRs (standardized mortality ratios) were.....suicide: 5.3&quot;</td>
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| Yes | "6 studies on heavy cannabis use and suicide attempt (OR 3.2)“ although included in this calculation was a study that involved more than 11 times of “ever use” which reported no significant increase, as compared to the Silins study reporting on daily use before age 17 (above).
Yes

A study that controlled for genetic and environmental confounders by analyzing twins


No


"The monozygotic twin who used cannabis frequently was more likely to report...suicidal ideation (OR 2.47) compared with their identical twin who had used cannabis less frequently, even after adjustment for covariates." Frequent cannabis use was designated as >100 times ever, much less than the daily use of the Silins et al. study of the cannabis-use disorder of the Arendt et al. study. As with all studies published to date on suicides (and unlike some of the research published on psychosis), the strength of the cannabis product was not assessed, though almost all of the suicide studies summarized in this talk likely pertained to the lower strength marijuana prevalent in the last century.

"Suicide was more common primarily in those who had used cannabis more than 50 times (OR 3.45), although this association was eliminated after adjustment for confounders...... The variables with the strongest confounding effects were problematic behaviour during childhood, other drug use, psychological adjustment, alcohol consumption, tobacco use and psychiatric diagnosis at conscription.” Studies that are outliers should be checked for how the methods differed from the others. Here, among the adjustments made, a possibly inappropriate 'collider' variable with marijuana use was created (see next slide). What this study did differently was control for tobacco use, which is very frequently an outcome of marijuana use. The Clarke et al. and Arendt et al. studies did not control for tobacco use and the Silins study only controlled for tobacco use that occurred in the pre-teen or early teenage years (earliest reports ages 10-13).
When correction for potentially confounding variables can create “collider variables”

Dependent variable

Suicide

Independent variable

Marijuana use

Psychiatric diagnosis at conscription

Independent variable

Smoking of tobacco
Dependent variable

**Suicide**

Independent variable

- Smoking of tobacco
- Psychiatric diagnosis at conscription

The link is strong for psychiatric diagnoses promoting cigarette use

The link is strong for marijuana use promoting cigarette use

"Collision" between the independent variables converge on smoking of tobacco: when two independent variables interact strongly with another independent variable used for correction; can potentially double the impact of correction in the above scenario.

When correction for potentially confounding variables can create “collider variables”
Dependent variable

Suicide

Independent variable

Marijuana use

Correcting for tobacco AND psychiatric diagnosis at conscription will inflate their impact and unduly weaken the calculated impact of marijuana use on suicide.

Why acute psychosis and acute suicidal urges may be much more likely to occur with edible marijuana products

Cannabidiol is degraded in gastric fluid, whereas THC is not

Why acute psychosis and acute suicidal urges may be much more likely to occur with edible marijuana products (continued)

Cannabidiol functionally antagonizes many effects of THC in animal models and in humans


**In mice**: “Chronic administration of THC during adolescence led to immediate and long-term impairments in object recognition/working memory.....All THC-induced behavioral abnormalities were prevented by the coadministration of CBD (cannabidiol).

**In humans**: “we tested the hypothesis that pre-treatment with CBD inhibited THC-elicited psychosis and cognitive impairment.... clinically significant positive psychotic symptoms (defined a priori as increases ≥3 points) were less likely in the CBD group (OR 0.22)
Why acute psychosis and acute suicidal urges may be much more likely to occur with edible marijuana products: the metabolite 11-OH-THC

Oral ingestion of dronabinol (a THC extract) that caused psychotic reactions was associated with higher levels of 11-OH-THC:

Favrat B et al. *Two cases of "cannabis acute psychosis" following the administration of oral cannabis.* BMC Psychiatry. 2005;5:17.

11-OH-THC is more potent in its psychiatric effects than is delta-9-THC:

From smoked marijuana, THC is more concentrated in plasma than 11-OH-THC

From oral marijuana, 11-OH-THC is more concentrated in plasma than THC


Why acute psychosis and acute suicidal urges may be much more likely to occur with edible marijuana products... (continued)
"Use of cannabis at baseline increased the risk for manic symptoms during follow-up (adjusted OR 2.7), adjusted for age, sex, educational level, ethnicity, single marital status, neuroticism, use of other drugs, use of alcohol, depressive symptoms and manic symptoms at baseline. The association between cannabis use and mania was independent of the prevalence and the incidence of psychotic symptoms. There was no evidence for reverse causality, as manic symptoms at baseline did not predict the onset of cannabis use during follow-up (OR = 0.35)."

"cannabis use selectively and strongly preceded and coincided with mania/hypomania"

cannabis use may worsen the occurrence of manic symptoms in those diagnosed with bipolar disorder, and may also act as a causal risk factor in the incidence of manic symptoms"
Is marijuana associated with the development of mania and bipolar disorder?..(continued)

Yes


"Regular cannabis use uniquely predicted the development of bipolar disorder, panic disorder with agoraphobia and social phobia."

versus (from same dataset):

No


"After adjusting for the covariates, cannabis use .. predicted increased prevalence and incidence of all .....substance use disorders, including nicotine dependence, but not of mood or anxiety disorders. “ What was different about the methods in this study? Included in the controls were individuals who had used marijuana up until one year before study onset, by which time the effect on risk for bipolar disorder may already have occurred. This approach might have lessened the difference in depression between marijuana using-cases versus controls.
Yes, panic but tobacco confounds


"Results indicated that cannabis use and dependence were significantly prospectively associated with an increased odds for the development of panic attacks and panic disorder. However, cannabis was not incrementally associated with the development of panic after controlling for daily cigarette smoking. Because marijuana use so often leads to cigarette use (the “reverse gateway” finding), it is often difficult to disentangle the two variables. Smoking of tobacco is also an independent risk factor for panic attacks.

Yes, panic


“Regular cannabis use uniquely predicted the development of...panic disorder with agoraphobia”. This study entered tobacco use as a covariate in the regression analysis; the association between tobacco use and panic disorder was found to be less robust than between cannabis and panic.

Yes, anxiety


"The results also confirm that after ingestion of delta-9-THC the volunteers experienced a large increase in the level of anxiety, which agrees with various previous descriptive reports". Anxiety was measured on self-reported scale of Spielberger’s State-Trait anxiety inventory. Co-administration of cannabidiol reduced the anxiety score by ½, but the rise in anxiety was still significantly greater than placebo. It was notable that cannabidiol did not block the increase in pulse rate triggered by THC.
Yes, anxiety and depression


“After controlling for confounding factors, those who started using cannabis before 15 years and used it frequently at 21 years were more likely to report symptoms of AD (anxiety and depression) in early adulthood (odds ratio 3.4).....This association was of similar magnitude for those who had only used cannabis and those who reported having used cannabis and other illicit drugs”.

Yes, depression


"Both early-onset and adult-onset cannabis smokers had a modest excess odds of a depression spell compared to never cannabis smokers, even with covariate adjustment (OR=1.7, OR=1.8, respectively)."

Yes, depression


"The OR for heavy cannabis users developing depression was 1.62" The results of this meta-analysis stem from studies employing a variety of correction factors.
"After adjusting for the covariates, cannabis use in wave 1 predicted increased prevalence and incidence of all wave 2 substance use disorders, including nicotine dependence, **but not of mood or anxiety disorders**“ In other words, **past-year use of marijuana in adults was not associated with depression.**

**What was different about his study?** Included in the controls individuals who had used marijuana up until one year before study onset, by which time the effect on depression risk may already have occurred. This approach might have lessened the difference in depression between marijuana using-cases versus controls.

"**After adjustment, the associations for depression and welfare dependence were both non-significant and negligible in size**“ Adjusted for 53 covariates (not listed in paper; referred to another paper); highly regarded study, thus effect of marijuana on depression may be small and/or confounded by other factors.

“**The monozygotic twin who used cannabis frequently was more like to report MDD (Major Depressive Disorder) odds ratio 1.98**...compared with their identical twin who had used cannabis less frequently, even after adjustment for covariates“ Despite controlling for many variables by comparing identical twins, adjusted for the following covariates which may have preceded or coincided with the onset of cannabis use: early alcohol use, early tobacco smoking, conduct disorder, and childhood sexual abuse.
The Concerns for PTSD

- "Veterans who were using marijuana at admission (continuing users and stoppers) had higher measures of violent behavior prior to admission than those who never used before or after the program."

- "Starters and continuing users had significantly higher measures of violent behavior at follow-up than all other groups."

- "After adjusting for covariates, in comparison to never-users, starting marijuana had an effect size on PTSD symptoms at follow-up of +0.34 (Cohen d = group difference/SD) and stopping marijuana use had an effect size of -0.18."

- "Significant associations as measured by standardized regression coefficients between change in days of marijuana used and change in PTSD symptoms, severity of violent behavior, the ASI alcohol index and the ASI drug abuse index."

Excluded subjects with problematic alcohol use, those with any drug use other than marijuana in the 30 days prior to admission, and those who entered treatment on transfer from an inpatient or residential program that would have restricted their access to drugs.
The Concerns for PTSD: potential benefit of marijuana for extinction of fearful memories?

Yes, THC


**Human studies**: "Compared to subjects that received PBO (placebo), subjects that received THC showed low SCR (skin conductance response) to a previously extinguished CS (conditioned stimuli) when extinction memory recall was tested 24 hours after extinction learning, suggesting that THC prevented the recovery of fear”

Yes, a CB1 agonist (like THC) but only at a low dose


**Animal studies**: “The administration of...WIN55,212-2.. facilitated the extinction of 24 h contextual fear memory” WIN mimics the effect of THC at the cannabinoid-1 receptor. But the facilitation of extinction occurred only at the lowest dose; the highest dose inhibited the extinction of contextual fear memory.

No, not THC if used chronically


**Human studies**: “In rats, chronic cannabinoid administration impairs fear extinction in a drug-free state. Here we examine whether chronic cannabis use is associated with impaired fear extinction in humans. Chronic cannabis use was associated with reduced within-session extinction of skin conductance response on Day 1 (d = 0.78), and between-session extinction on Day 2 (d = 0.76)”
The Concerns for PTSD: also a negative impact of marijuana on positive memories and the reward circuit?

**Yes, inhibits positive memory associations**


Human studies: “THC significantly impaired memory performance overall.....THC significantly impaired memory for positive pictures, and it also tended (to a lesser extent) to impair memory for negative pictures, but did not affect memory for neutral pictures”

**Yes, inhibits positive memory associations**


Human studies: "Relative to placebo cannabis, active cannabis reduced liking of cannabis-associated stimuli“ This trend did not hold true for pictures of food.

**Yes, inhibits positive reward component**


Human studies: “ Compared with placebo, cannabis without cannabidiol dampened response to music in bilateral auditory cortex (right: P=.005, left: P=.008), right hippocampus/parahippocampal gyrus (P=.025), right amygdala (P=.025), and right ventral striatum (P=.033).... These findings were contrary to our prediction that cannabis would increase the rewarding effects of music...It should also be noted that our findings of dampened response to music occurred in the context of increased wanting to listen to music. These findings are broadly consistent with previous findings that THC may have dissociable effects on anticipatory (“wanting”) and consummatory (“liking”) components of reward”
The Concerns for PTSD: is cannabidiol effective in extinction of fearful memories?

Yes


Human studies: “These findings provide the first evidence that CBD can enhance consolidation of extinction learning in humans and suggest that **CBD may have potential as an adjunct to extinction-based therapies for anxiety disorders**”

Yes


Animal studies: “These results highlight that recent and older fear memories are equally vulnerable to disruption induced by CBD (cannabidiol) through reconsolidation blockade, with a consequent long-lasting relief in contextual fear-induced freezing....CBD-induced fear memory disruption does not show reinstatement”

Yes, but only when the fear is strong


Animal studies: “in the more translationally-relevant stronger conditioning setting, **CBD both acutely inhibited fear expression and enhanced extinction to produce longer lasting reductions in fear**”
CONCLUSIONS

- **Marijuana containing Δ⁹–THC poses substantial risks** for mental, cardiac and neonatal health, and for several types of cancer as determined by tissue-specific receptor differences. Any benefit has to be weighed against these risks.

- **For non-neuropathic pain**, there is little evidence for benefit of cannabidiol and/or Δ⁹–THC (failed in clinical trials); when used as adjunctive therapy, the opiate dose required is not reduced.

- **For neuropathic pain**, a variable degree of relief can occur in some individuals; cannabidiol-rich preparations may be most effective and certainly the safest.

- **For the treatment of spasticity in multiple sclerosis**, preparations rich in Δ⁹–THC may offer benefit, but can accelerate the cognitive decline of the disease and cause dizziness (further impairs mobility).

- **For some children with intractable epilepsy**, cannabidiol holds promise as an adjunctive anticonvulsant; the route of administration requires some optimization; FDA should review.

- **Pharmaceutical companies are aggressively working on more specific drugs** to surpass marijuana in the future, because of undesirable activity of Δ⁹–THC.
During the time when Colorado just had medical marijuana, 74% of teens entering treatment for marijuana abuse in Denver reported they obtained their marijuana from someone with a medical marijuana card. Selling to youth was not occurring in dispensaries, rather they were obtaining marijuana the same way teens currently get alcohol in our state, from someone who could legally purchase it.