

## Opioid Sparing Effects of Cannabis

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Director of Neurological Services  
North American Partners in Pain Management  
Can Medical Cannabis help with the Opioid Crises?

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## Cannabis Plant



- **Bud**
  - Cultivated and trimmed portion of female flower
- **Trichomes**
  - Hairlike outgrowths that secrete terpenes and cannabinoids

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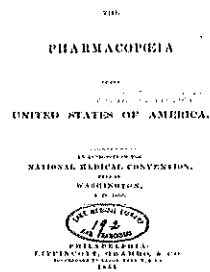
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## US Pharmacopeia 1851

- **Cannabis**
  - Alcoholism
  - Neuralgia
  - Opiate Addiction
  - Insanity
  - Convulsive disorders
  - Gout
- [Antiquecannabis.com](http://Antiquecannabis.com)



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- "Marijuana in its natural form is one of the safest therapeutically active substances known to man. By any measure of rational analysis marijuana can be safely used within a supervised routine of medical care. ... It would be unreasonable, arbitrary and capricious for DEA to continue to stand between those sufferers and the benefits of this substance in light of the evidence in this record."

---DEA Chief Administrative Law Judge Francis L. Young, Ruling in the matter of Marijuana Rescheduling Petition, September 6, 1988

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### Medical Marijuana for Opiate Addiction

- In 1889, writing in The Lancet about his experience helping patients addicted to pain medications, Dr. Edward A. Birch stated: "I prescribed the cannabis simply with a view to utilizing a well-known remedy for insomnia, but it did much more than procure sleep. I think it will be found that there need be no fear of peremptorily withdrawing the deleterious drug, if hemp is employed."

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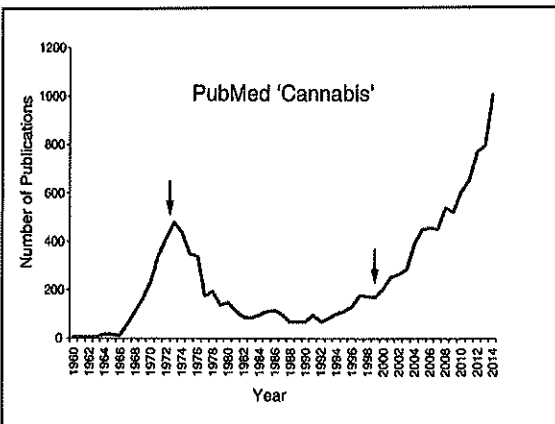
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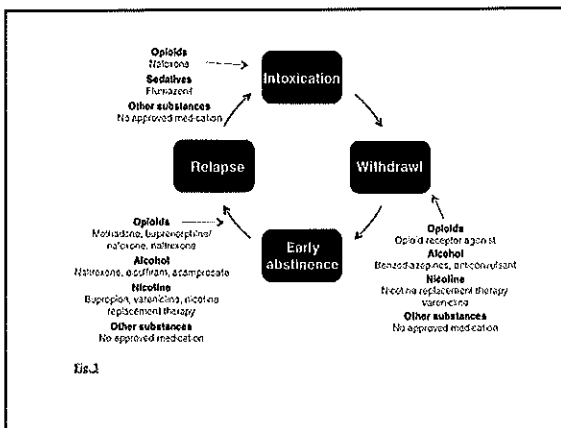
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- THC has been shown to be rewarding and to enhance the sensitivity of other drugs
  - CBD
    - Low reinforcing properties
    - Limited abuse potential
    - Inhibit drug seeking behavior
  - CBD anxiolytic properties and minimal side effect profile supports its potential viability as a treatment option for a variety of symptoms associated with drug addiction
  - Most available medications used for treating addiction have low to moderate effects on relapse outcomes
  - CBD's effects were prolonged, lasting two or more weeks after administration in its efficacy to reduce heroine reinstatement behavior triggered by drug-specific environmental cues. Even when it was administered during active heroine intake, the ability of CBD to inhibit relapse behavior was still apparent weeks after exposure.
- Yarosh, L. Hunt et al. Early Phase in the Development of Cannabis as a Treatment for Addiction: Opioid Relapse Test in a Pre-Clinical Stage. *Neuropharmacology*. 2015 Oct; 100: 879-815

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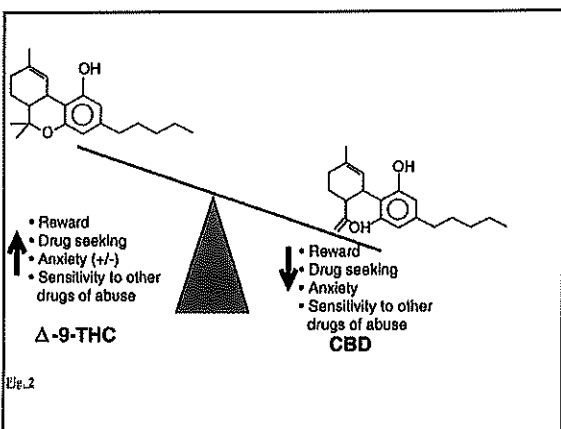
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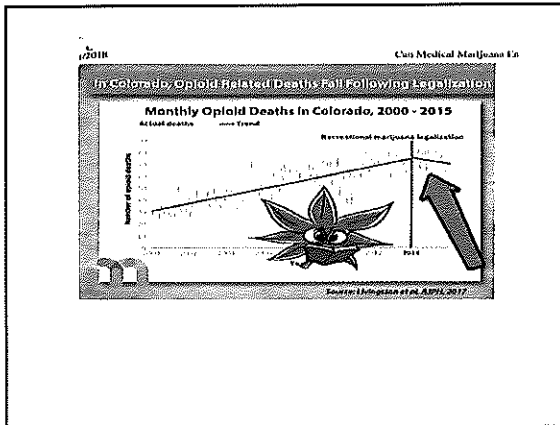
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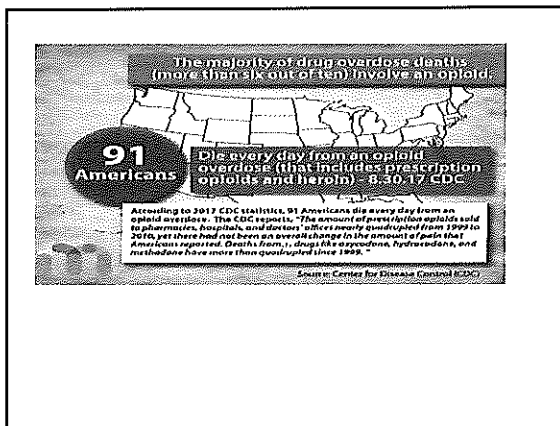
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**Pharmaceutical companies and cannabis**

- In 2016 Insys therapeutics gave half a million dollars to the campaign to stop marijuana legalization in Arizona
- Of the five states with adult-use cannabis legalization on the ballot in 2016, Arizona was the only place where it didn't pass.
- Big Pharma spent \$880 million nationwide on political donations and lobbying against legalization of marijuana between 2006 and 2015

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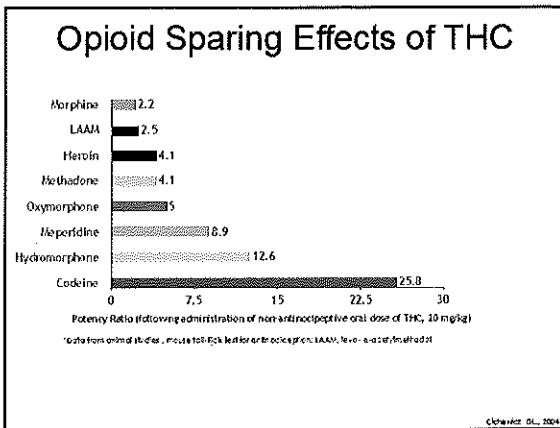
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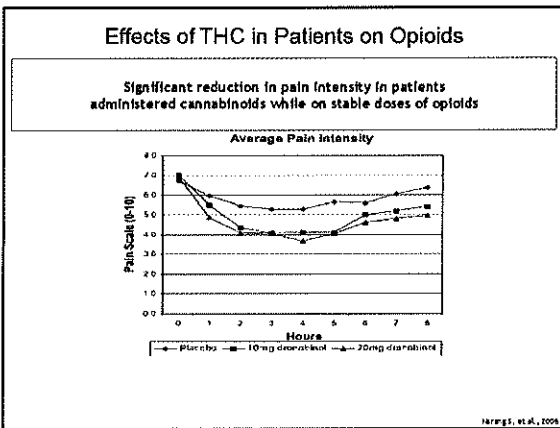
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### Association between medical cannabis and prescription opioid use in chronic pain patients: a preliminary cohort study

- 21 month observational period
- Chronic pain patients, mainly LBP.
- Chronic opioid users. PMP was used
- Patient's decision to use cannabis
- All patients had the opportunity to use medicinal cannabis, (37 MCP) 29 (non MCP)
- All opioids were first normalized into milligrams of IV MSO4 using the GlobalRPH equivalency calculator and IV:Oral 3:1 was used to measure patient's consumption levels.

• Hoch M, et al. 2017. (211) Association between medical cannabis and prescription opioid use in chronic pain patients: a preliminary cohort study.

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Table 1

Variable (N = 66)	Comparison (N = 29)	MCP (N = 37)	P Value
Ceased opioid prescriptions (0,1)	3.4% (1)	40.5% (15)	< 0.001
Reduced prescribed daily opioid dosage (0,1)	41.8% (13)	83.8% (31)	0.001
Average daily opioid dosage in the last 3 months (mg)	16.2 ± 14.8	23.4 ± 23.3	0.103
Average daily opioid dosage in the last 3 months (mg)	12.3 ± 12.4	12.4 ± 20.1	0.974
Change in prescribed daily opioid dosage (mg)	-3.9 ± 13.2	-32.0 ± 23.4	0.181
Percentage point change in prescribed daily opioid dosage	10.4 ± 114.9	-42.0 ± 65.1	0.013
Male	54.1% (20)	69.0% (20)	0.219
Age	59.7 ± 13.6	53.6 ± 9.5	0.036

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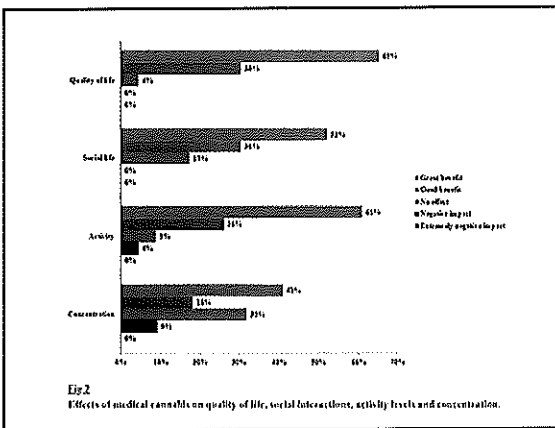
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### Risk of Cannabis Dependency

- Cannabis 6.2% < Alcohol 11.2% < Nicotine 36%

• Liu YH et al., Disease-based Therapies Opioid-Cannabis Dependency. Clin Journal. 2015 Sept; 115(9): 652-659

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**Cannabis as a substitute for prescription drugs- a cross sectional study**

- To examine whether and how often cannabis users reported substituting cannabis for prescription drugs
- Individuals were substituting cannabis for prescription drugs independent of whether they identified themselves as medical users
- 1,248 respondents reported 2,473 substitutions
- The comorbidity triad of pain, anxiety and depression was associated with greater substitution frequency

• James H Corroon, Jr et al. Cannabis as a substitute for prescription drugs- a cross sectional study

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**Medical cannabis access, use and substitution for prescription opioids and other substances: a survey of authorized medical cannabis patients**

- Respondents were allowed to report up to three medications for which they substituted cannabis
  - 59% reported substituting for a single class of medication
  - 33% reported substituting for two classes
  - 8% reported substituting for three classes
- The most common substitution was for opioids 32%, followed by benzodiazepines 16% and antidepressants 12%
- The reasons most frequently ranked as being most important for substituting cannabis for prescribed medications were "less adverse side effects" 39%, "cannabis is safer" 27% and "better symptom management" 16%.

• Philippe Lucas et al. International Journal of Drug Policy 42 (2017)30-35

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### Prescription and recreational use

- Unlike opioids where medical use via prescription often precedes recreational use and dependence, the pathways between the medical and recreational use of cannabis are reversed, with previous recreational use often a precursor to prescription medical use, while the reverse is rarely the case.
- 81% of participants in the study had experience with marijuana before using it for medicinal purposes, however, less than 3% of patients who started using it for medicinal purposes transitioned to recreational use.

• Philippe Lucas et al, International Journal of Drug Policy 42 (2017)30-35  
 • Fischer et al 2009

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### Cannabis use is associated with lower rates of initiation of injection drug use among street-involved youth: A longitudinal analysis

- 481 at risk youth age 14-26 from Vancouver were studied from 9/2005-5/2015
- Open prospective cohort study
- Results
  - 47.4% reported at least daily cannabis use and 21.4% initiated injection drug use.
  - Multivariable analysis showed that greater cannabis use was associated with slower rates of injection initiation (P=0.038)

• Hudson Reddon et al, Drug and Alcohol Review (March 2018), 37, 421-428

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### CBD and Neurobiological Targets/Effects

- CBD decreases stress and exhibit anxiolytic-like effects via its 5HT<sub>1A</sub> receptor modulating properties
- It also has panicolytic properties
- It acts as an antidepressant in animal models of depression and decreases compulsive behaviors in rodents
- CBD was shown to prevent cocaine-induced hepatotoxicity, reverse binge ethanol-induced neurotoxicity and mitigate the cardiac effects of THC
- It is known to attenuate amphetamine-induced hyperlocomotion
- These actions are hypothesized to be linked to CB<sub>1</sub> related mechanisms

• Yoonan L. Hart et al Early Phase in the Development of cannabidiol as a treatment for addiction, opioid response times from center stage Neuropharmacology 2015 Oct 15; 124(4):807-815

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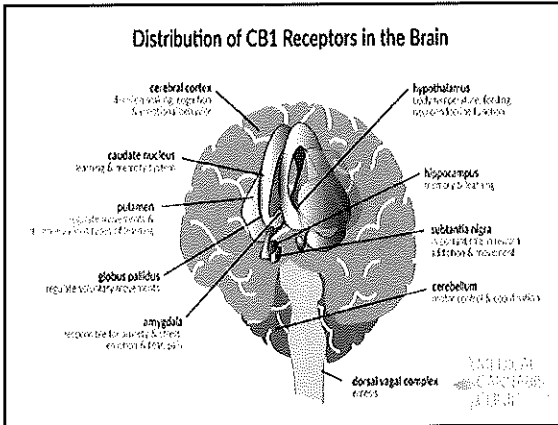
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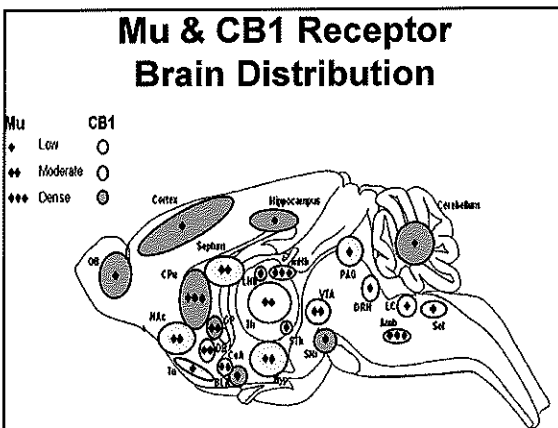
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### The Endocannabinoid System as a Treatment Target for Addiction

- Type 1 cannabinoid receptors (CB<sub>1</sub>R) are co-localized with opioid receptors in striatal output projection neurons of the nucleus accumbens and dorsal striatum that modulate reward, goal-directed behavior and habit formation relevant to addiction.\*
- Type 2 cannabinoid receptors (CB<sub>2</sub>R) have very low expression in the brain generally, but recently they have been shown to be expressed in dopamine neurons of the midbrain ventral tegmental area and modulate the functional excitability of dopamine neurons central to addiction related behaviors such as drug reinforcement\*\*

\*Fragdoux JF et al. Ultrastructural localization of CB1/Cannabinoid receptors in opioid receptor patches of the rat nucleus accumbens. *J Neurosci* 2003; 23: 1123-1133.  
 \*\*Zhang JY et al. Cannabinoid CB2 receptors modulate cocaine dependence neuronal activity and dopamine release behavior in mice. *Proc Natl Acad Sci USA* 2014; 111: 8200-8205.

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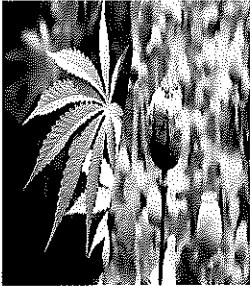
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## Opioid & Cannabinoid Similarities & Interactions



- Receptors are located presynaptically
- Coupling of some G protein
  - Inhibition of adenylyl cyclase
- Blockage of voltage dependent Ca<sup>++</sup> channels
- Activation of voltage dependent K<sup>+</sup> channels
- THC can enhance mu opioid anti-nociceptive effect- Pugh 1996
- Cannabinoids can increase release of endogenous opioids - Smith 1998
- Vaporized cannabis may allow lower opioid dose with fewer AE's - Abrams 2011

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## CBD in Preclinical Addiction Models

- CBD does not have hedonic properties on its own. It is not rewarding and does not induce drug-seeking behavior.
- CBD does not promote conditioned place preference or increase the reinforcing efficacy of brain stimulation, which are both definitive characteristics of addictive substances.
- There is also evidence to show that CBD could inhibit relapse behavior and the effect can last for weeks. This property is unique to CBD and is not found in the medications currently used to treat drug abuse
- CBD also reduces morphine withdrawal symptoms (e.g., wet shakes, diarrhea, ptosis, teeth chattering, etc)

• Thomas L. Hull et al. *et al.* *Effects of the Development of conditioned aversive structures for addiction: opioid seeking and relapse after drug Neuropharmacology 2013 Oct 1; 76(1):202-11.*

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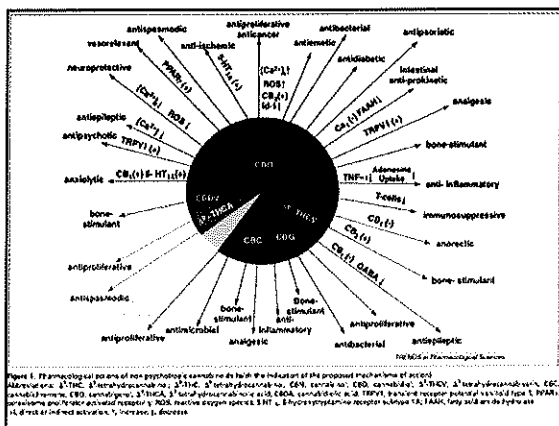
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### Cannabis use in Cancer and Palliative Care

- Chemotherapy-induced nausea and vomiting
- Cancer-associated pain
- Anorexia and cachexia syndrome
- Insomnia
- Depression and anxiety
- Cannabis as an anti-neoplastic agent

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### Cannabis as an Anti-Neoplastic Agent

- Connection to cancer cell signaling pathways
    - It has been shown to induce apoptosis and inhibit tumor proliferation, vascularization and metastasis.
  - In Non-small cell lung carcinoma, administration of Δ9-THC inhibited endothelial growth factor-induced migration in vitro, as well as tumor and metastasis growth in mice models.
  - In murine glioma, CBD had anti-proliferative effects, and selective CB<sub>2</sub> agonist caused tumor regression.
  - Activation of CB<sub>1</sub> in mice with colon carcinoma reduced tumor growth.
  - Treatment with cannabinoids has also been associated with reduced tumor growth in models of breast cancer, hepatocellular carcinoma, and multiple hematological malignancies
  - Pure CBD is being investigated as single-agent therapy for solid tumors.
- Wessli G et al., The use of cannabinoids as anticancer agents [Review]. Prog Neurobiopharmacol Biol Psychiatry 2016 61:258-66

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### Cannabinoids and Cancer Therapy

- There is evidence that cannabinoids may have anti-cancer effects. This was noted in lung adenocarcinoma models in the 1970s\*
  - Studies have demonstrated tumor growth inhibition in vitro and in vivo in glioblastoma multiforme, breast, prostate, thyroid, colon, skin, pancreatic, leukemia and lymphoma models.\*\*
  - The exact mechanism by which this anti-tumor effect occurs may involve suppression of proliferative cell signaling pathways, inhibition of angiogenesis and cell migration, stimulation of apoptosis, and/or induction of autophagy.
- \* Munson AE et al., Antineoplastic activity of cannabinoids. J Natl Cancer Inst 1975;65:587-602.  
 \*\* Pappas S et al., Use of cannabinoid receptor agonists in cancer therapy as palliative and curative agents. Best Pract Res Clin Endocrinol Metab 2009;23:117-31.

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### Common Misconceptions

- No evidence-based studies demonstrating that chronic cannabis use can cause or exacerbate schizophrenia
- Smoking cannabis is not associated with an increased risk of developing COPD or lung Ca
  - In fact, protective effects of cannabis smoking seen in two large retrospective, population-based case-control studies

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### Adverse Effects

- No risk of lethal overdose, end-organ damage/labs to follow
- "except for...smoking, the adverse effects ... within the range of effects tolerated for other medications" (IOM)
- "few... develop dependence... Risk factors... similar to ... other forms of substance abuse... antisocial personality and conduct disorders..."
- "distinctive... withdrawal syndrome... identified... mild and short-lived... restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping"
- Review of 31 clinical studies of medical cannabinoids:
  - 98.6% of adverse events reported were not serious
  - "164 serious adverse events"—"no evidence of a higher incidence of serious adverse events... compared with control [drugs]" .

\*Wang T, Collet J, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. Canadian Medical Association Journal 2008; 178(13):1669-1678.

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### Drug Interactions Cytochrome P 450 Enzymes

- THC and CBD are metabolized by CYP 3A4 and CYP2C9 (Yamori et al 2012; Watanabe et al 2007)
  - CYP 3A4 *Inhibitors slightly increase* THC levels
  - CYP 3A4 *Inducers slightly decrease* THC and CBD levels

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**Drug Interactions  
Cytochrome P450 Enzymes**

- **THC is a CYP1A2 inducer**
  - THC can potentially decrease serum concentrations of
    - clozapine, duloxetine, naproxen, cyclobenzaprine
- **CBD is a potent inhibitor of CYP 3A4 and CYP2D6**
  - CBD via CYP3A4 may increase serum concentrations of
    - Benzos, antihistamines, calcium channel blockers
  - CBD via CYP2D6 may increase serum concentrations of
    - SSRIs, TCAs, b-Blockers, antipsychotics and opioids

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**Marijuana Effective Drug  
Safety (MEDS) Act of 2017**

- Senator Hatch introduced a bill in September 2017 to address the opioid crises
  - <http://www.hatch.senate.gov/public/index.cfm/2017/9/hatch-introduces-medical-marijuana-research-bill>
- While legislation proceeds, many doctors in the 29 states and Washington DC with legal medical marijuana are already collecting data on Cannabis use
  - <http://medicalmarijuana411.com/marijuana-legal-in-your-state/>

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**The Marijuana Justice Act**

- Senators Kirsten Gillibrand and Corey Booker are cosponsoring this bill
- February, 14<sup>th</sup> 2018

thehill.com/regulation  
<https://hightimes.com>

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### Summary

- Medical marijuana represents a complex chemical mixture, all of which may not be appropriate treatment for substance abuse disorder. While one cannabinoid constituent in the plant can alleviate negative symptoms, another may exacerbate them. It is important to emphasize that it is specific cannabinoids, such as CBD, that may hold the medicinal promise, not the general marijuana plant.
- As more research efforts are directed towards cannabinoids, we will soon be able to understand how best to leverage the potentially beneficial properties of cannabinoids to develop more targeted treatment interventions

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### Summary (Cont)

- Research suggest that cannabis can be used as an exit drug to reduce the use of substances that are more harmful, including opioids, benzodiazepines, alcohol and cocaine. This is why modern science is now viewing cannabis more as a terminus drug than the gateway drug it was long rumored to be.

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