Opioids, Cannabis, and Chronic Pain: What Doctors Do & Don't Know

James Wolf, M.D., Assistant Professor of Anesthesiology

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Topics for discussion:

Opioids and the "Opioid Crisis"

- How do opioids work?
- Why do some people experience chronic pain while other people's pain just resolves?
- How did this whole opioid crisis thing start? Is it really all our (doctors') fault?
- Are things getting better or worse?
- How are we ultimately going to fix this?
- How do we decide if a therapy is good or bad (in general)?

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Cannabis

According to my Uncle David and the internet, it is:

- 1. Totally awesome
- 2. Completely safe
- 3. Scientifically proven to cure ALL
  - Pain, anxiety, PTSD, cancer, infections, vaccine side-effects, Congressional gridlock and demonic possession.

Is that true?

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Goals and Objectives:

1. A Better Thanksgiving for Doctors.

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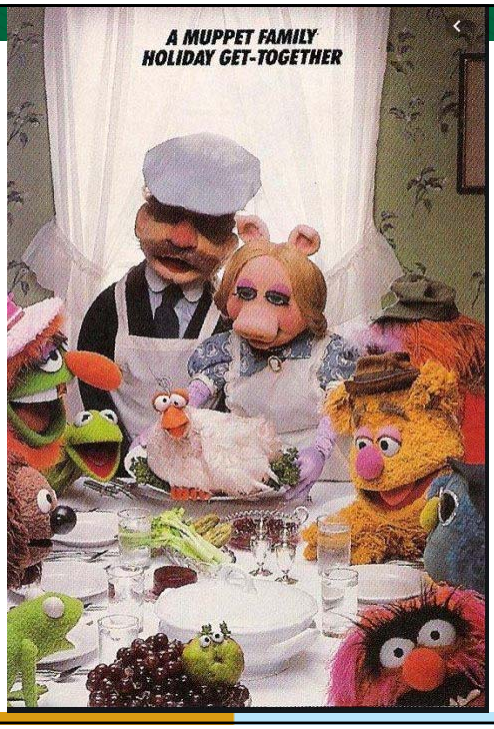

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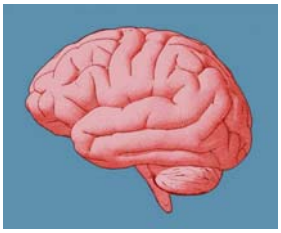
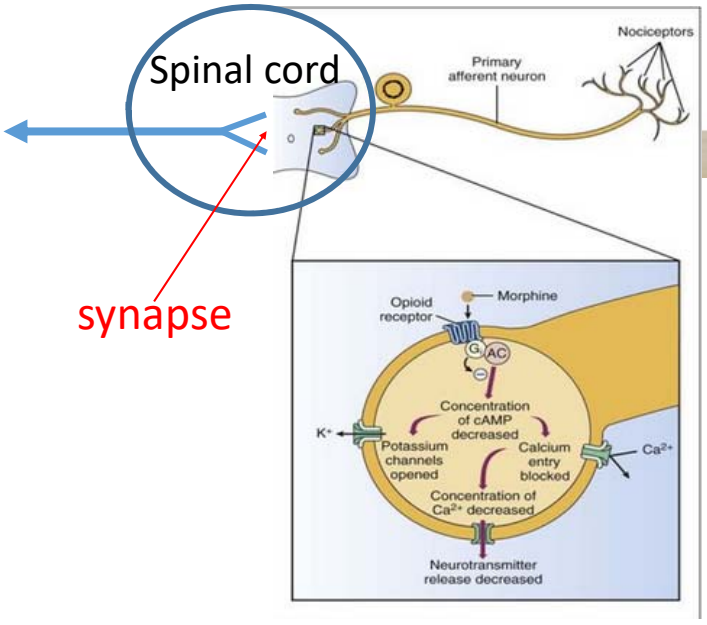
How do Opioids Work?





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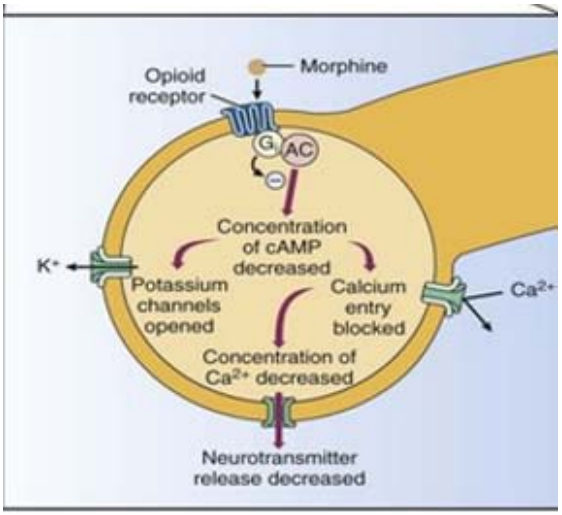
How do Opioids Work?



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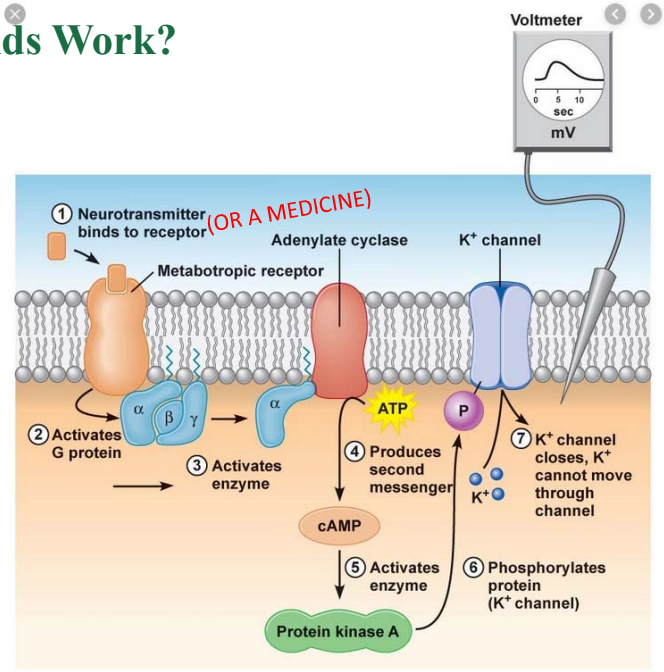
How do Opioids Work?



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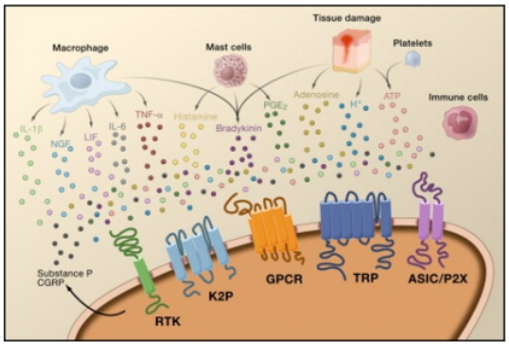
What is "chronic" pain?

Peripheral sensitization

- Peripheral sensitization (primary hyperalgesia) is a reduction in threshold and an increase in responsiveness of the **peripheral ends of nociceptors**
  - Ex. The change in heat sensitivity after sunburn, when a normally warm stimulus feels burning hot in the sunburned areas
  - Occurs with injury or in certain disease states such as diabetes
- Sensitization arises due to the action of **inflammatory chemicals** released around the site of tissue damage (histamine, bradykinin, serotonin, ATP, *prostaglandins*, *cytokines, chemokines* etc…)
  - **These chemicals can bind to receptors on the distal peripheral nerves and depolarize them closer to threshold**
  - **Persistent stimulation can also lead to an increase in Na+ channel number and subtype, and TRP channels, resulting in stronger depolarization events**



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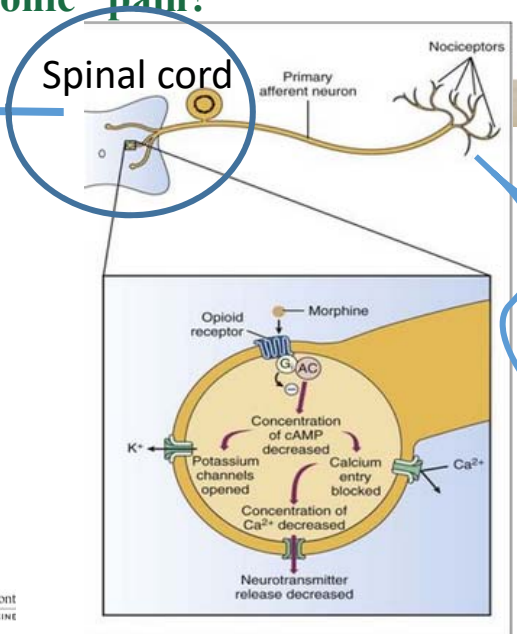
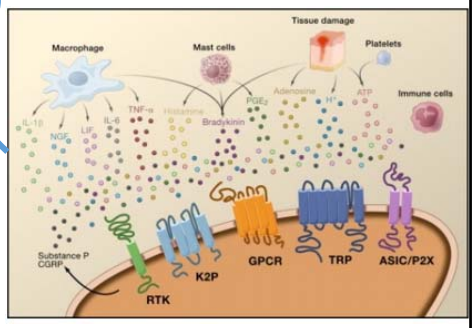
What is "chronic" pain?





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What is "chronic" pain?

Central sensitization

- Central sensitization is an **increase in the excitability of neurons within the central nervous system,** either due to peripheral or central nerve damage and inflammation AND OTHER THINGS LIKE OPIOIDS AND ANXIETY

- Normal inputs begin to produce abnormal responses
  - A burst of activity in nociceptors **alters the strength of synaptic connections** between the nociceptor and the neurons of the spinal cord (hyperalgesia)
  - Low-threshold sensory fibers activated by light touch begin to activate neurons in the spinal cord that normally only respond to noxious stimuli (allodynia)

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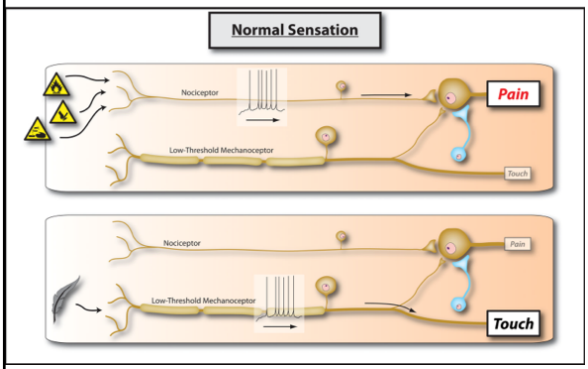
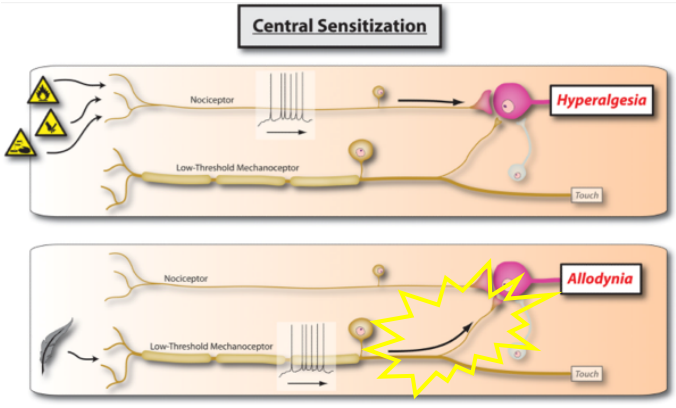
What is "chronic pain"?"





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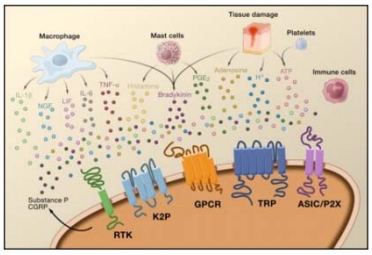
What is "chronic" pain?

OPIOIDS AND ANXIETY



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Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

2018 ANNUAL SURVEILLANCE REPORT OF DRUG-RELATED RISKS AND OUTCOMES

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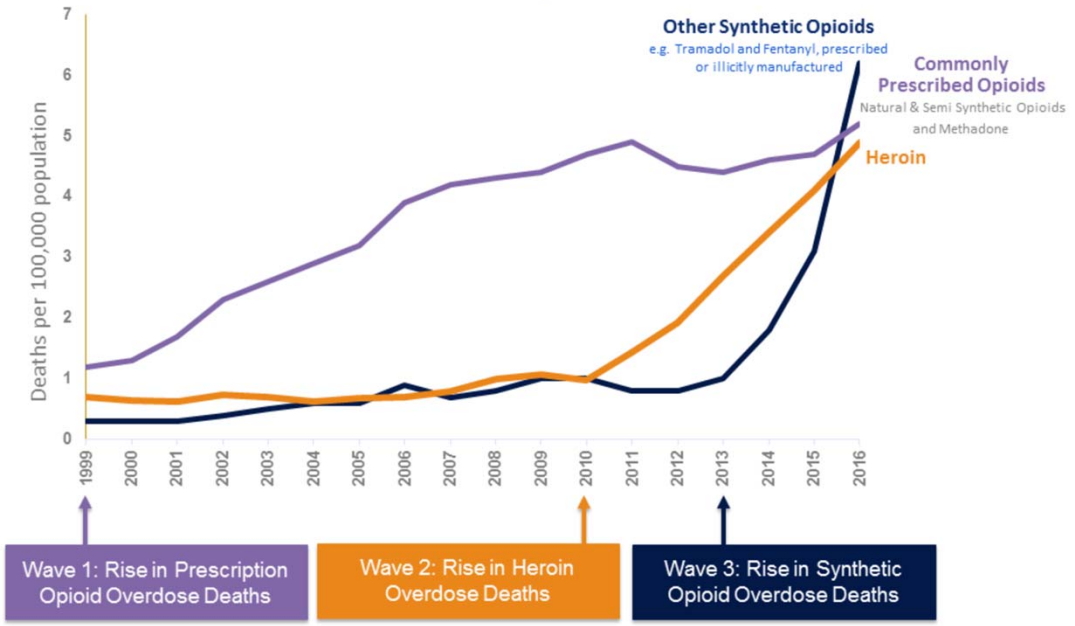
3 Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.

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ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients[1] who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,[2] Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

This letter to the editor is presented in its entirety.

It has been cited nearly 1000 times.

Sample citation:
"Therapeutic use of opiate analgesics rarely results in addiction."

NEJM. 1980;302(2):123.
JAMA. 2017; 317(11):117-8.
AIM. 1990;113:885-889.

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Baby Shark Dance | Sing and Dance! | Animal Songs | PINKFONG
https://www.youtube.com/watch?v=XqZsoesa55w

Lyrics
Baby shark, doo doo doo doo doo doo
Baby shark, doo doo doo doo doo doo
Baby shark, doo doo doo doo doo doo
Baby shark!... More

Available on

ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

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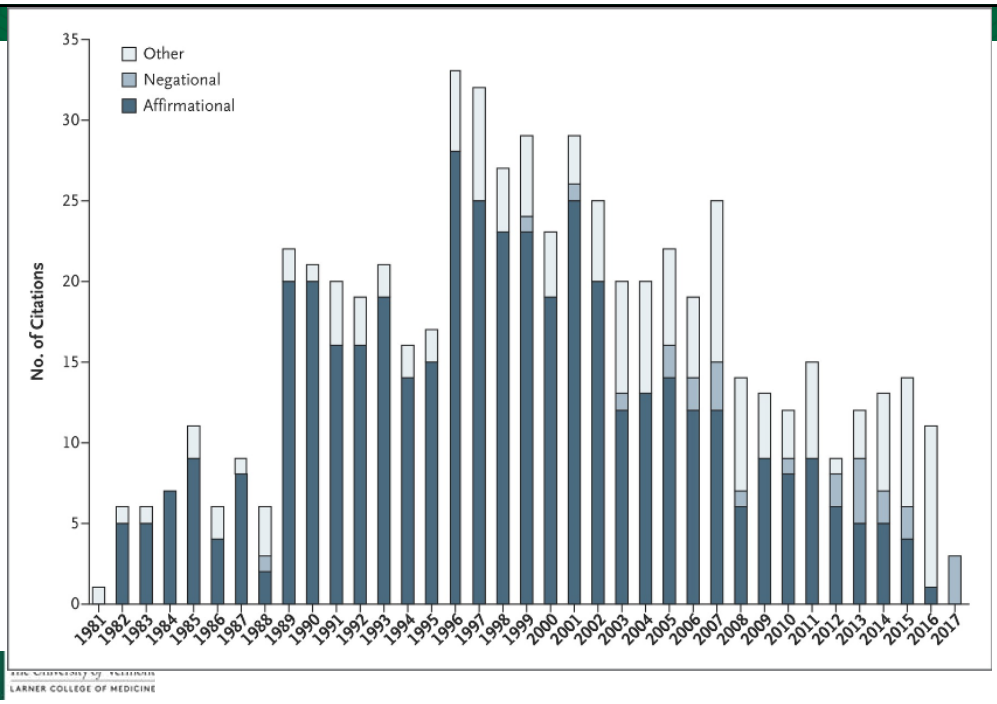

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- In conclusion, we found that a five-sentence letter published in the *Journal* in 1980 was heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy.

- We believe that this citation pattern contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers' concerns about the risk of addiction associated with long-term opioid therapy.

- In 2007, the manufacturer of OxyContin and three senior executives pleaded guilty to federal criminal charges that they misled regulators, doctors, and patients about the risk of addiction associated with the drug.

- Our findings highlight the potential consequences of inaccurate citation and underscore the need for diligence when citing previously published studies.

Leung, P. T., Macdonald, E. M., Stanbrook, M. B., Dhalla, I. A., & Juurlink, D. N. (2017). A 1980 letter on the risk of opioid addiction. *New England Journal of Medicine, 376*(22), 2194–2195.

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Opioid Prescribing Practices

Total number and rate of opioid prescriptions[a] (Rx) dispensed per 100 persons annually — United States, 2017

Opioid prescriptions (Rx)	Number	Rate[b]
All opioids	191,146,822	58.5
LA/ER opioids[c]	17,442,895	5.3
Days of supply per Rx		
< 30 days	110,759,830	33.9
≥ 30 days	80,386,991	24.6
Average opioid Rx per patient	3.4	
Average days of supply per Rx	18.3	

Source: IQVIA™ Transactional Data Warehouse.
Abbreviation: Rx, prescription.
[a]Opioid prescriptions, including codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, propoxyphene, tapentadol, tramadol, and Butrans® and Belbuca® (buprenorphine), were identified using the National Drug Code.
[b]Rate per 100 persons.
[c]LA/ER represents opioids that are long acting (LA) or extended release (ER).

2006
72.4
- 19.2%

•A total of 166,941,732,435 MME (i.e., the total dosage or amount of opioids prescribed accounting for differences in drug type and strength) were prescribed in 2017.

•The average dosage per prescription was 873.4 MME, and the average daily dosage per prescription was 45.3 MME.

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Average days of supply per prescription

Between 2006 and 2016, average days of supply per prescription increased from 13.3 to 18.3 days, an overall relative increase of 37.6%. The rate increased annually by 4.1% (95% CL: 3.9, 4.4) from 2006 to 2009, by 2.9% (95% CL: 2.7, 3.2) from 2009 to 2013, and by 2.1% (95% CL: 2.0, 2.3) from 2013 to 2017.

Average daily dosage (MME/day) per prescription

Between 2006 and 2017, the average daily MME per prescription decreased from 59.7 to 45.3 for all opioids, an overall relative reduction of 24.1%. The rate decreased annually by 1.0% (95% CL: -1.2, -0.8) from 2006 to 2010, by 4.5% (95% CL: -5.1, -3.9) from 2010 to 2013, and by 2.2% (95% CL: -2.4, -2.0) from 2013 to 2017.

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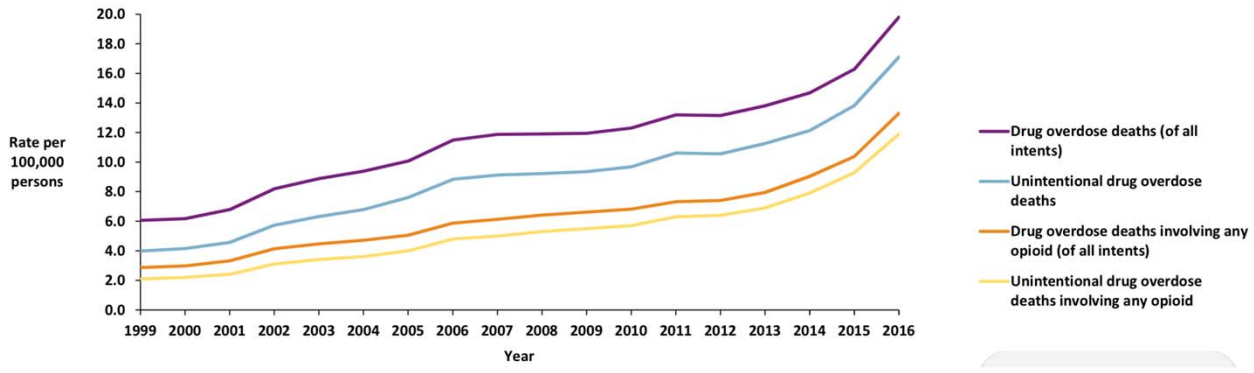
Age-adjusted rates of drug overdose deaths[a] and drug overdose deaths involving any opioid[b] for all intents and for unintentional intent by year — United States, 1999–2016



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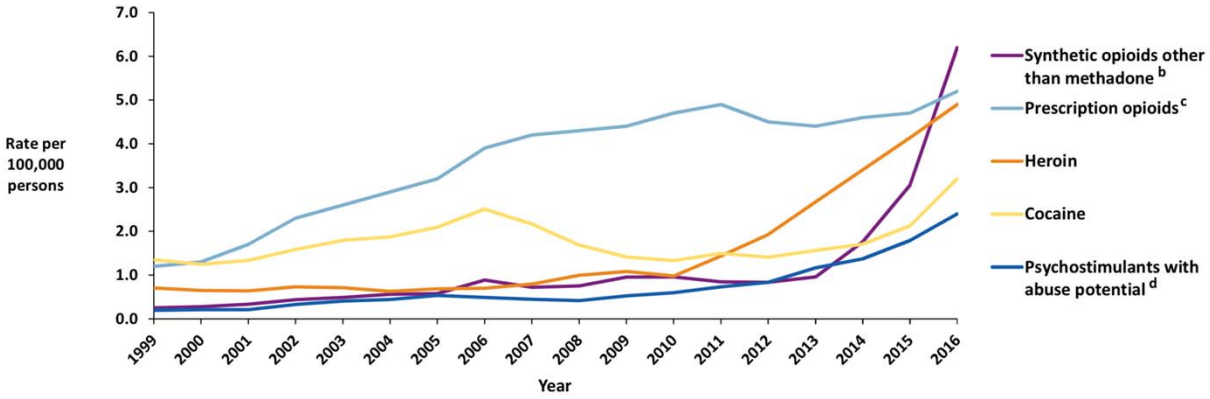
Age-adjusted rates[a] of drug overdose deaths by drug or drug class and year — United States, 1999–2016



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- In 2016, an estimated 11,824,000, or 4.4% of persons aged 12 and older, reported opioid misuse in the past year
- In 2016, an estimated 2,144,000, or 0.8% of persons aged 12 and older, reported an opioid use disorder in the past year
- In 2016, an estimated 948,000, or 0.4% of persons aged 12 and older, reported heroin use in the past year
- In 2016, an estimated 626,000 persons, or 0.2% of persons aged 12 and older, reported a substance use disorder in the past year involving heroin
- In 2016, an estimated 11,517,000, or 4.3% of persons aged 12 and older, reported misuse of prescription pain relievers in the past year
- In 2016, an estimated 1,753,000, or 0.7% of persons aged 12 and older, reported a substance use disorder in the past year involving misuse of prescription pain relievers

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In 2016, 2,181,000 persons, or 0.8% of persons aged 12 and older, reported that they had received illicit or prescription drug treatment in the past year at any location, such as a hospital (inpatient), rehabilitation facility (inpatient or outpatient), mental health center, emergency room, private doctor's office, self-help group, or a prison or jail.

In 2016, 1,406,000 persons, or 0.5% of persons aged 12 and older, reported that they had received illicit or prescription drug treatment in the past year at a specialty facility, which includes a hospital (inpatient only), rehabilitation facility (inpatient or outpatient), or mental health center.

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What is Cannabis?

Cannabis – contains over 100 distinct cannabinoids

- Cannabinoids – compounds acts on a cannabinoid receptor

THC – Tetrahydrocannabinol

- Naturally occurring (-) trans isomer of delta-9-tetrahydrocannabinol
- Primary psychoactive component

CBD - Cannabidiol

- No psychoactive effects
  - Mitigates THC psychoactive effects
- Anti-emetic, anti-inflammatory properties

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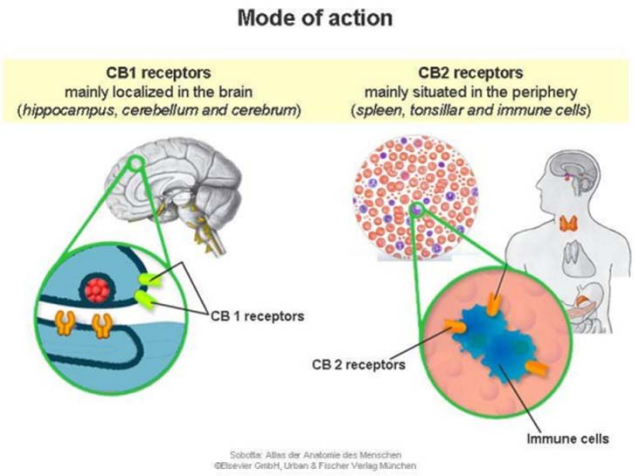
Cannabinoid Receptor 1

CB1 – expressed predominantly in th

Central Nervous System

- Inhibits the release of GABA, Glutamate, glycine, CCK, norepi, histamine
- Responsible for the psychotropic effects
- Increased expression in the thalamus, DR spinal cord in disease
- Inhibits gastrointestinal activity
- Induces ghrelin release → induces overeating
- Increases dopamine release from the nucleus accumbens with food intake



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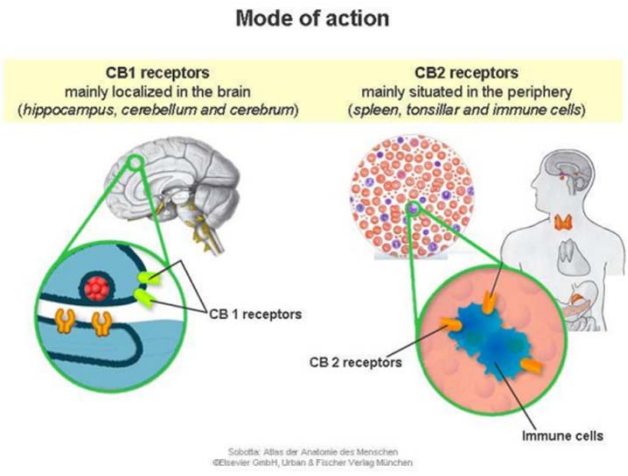
Cannabinoid Receptor 2

CB2 – expressed mainly in the

immune system/RBCs

- Induction of apoptosis and cell migration
- Changes in CB2 expression reported in nearly all disease states
- Decreases dopamine release in cocaine use
- Modulates the intestinal inflammatory response in IBD



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For Chronic Pain in General?

18 double or triple blinded RCTs

14 studies were vs. placebo
4 studies were vs. analgesic vs. placebo

Effect size for cannabis was -0.61
- The mean pain report in in each group differed by 0.61 standard deviations.
- 0.5 is a "medium effect size"
- 0.8 is a "large effect size"

PAIN MEDICINE
Volume 10 · Number 8 · 2009

REVIEW ARTICLE

Systematic Review and Meta-analysis of Cannabis Treatment for Chronic Pain

Eva Martín-Sánchez, MSc,* Toshiaki A. Furukawa, MD,§ Julian Taylor, PhD,† and Jose Luis R. Martin, PhD*‡

*Department of Clinical Research, Castile-La Mancha Health Research Foundation (FISCAM), †Department of Experimental Neurology and ‡Department Applied Research, National Hospital for Paraplegics, Toledo, Spain; §Department of Psychiatry, Nagoya City University, Medical School, Nagoya, Japan

Numbers Needed to Harm:
- Euphoria = 8, Dysphoria = 29
- "Alterations in Perception" (visual hallucinations, disorientation, confusion, dissociation, acute psychosis) = 7
- Motor Function (speech speech disorders, ataxia, muscle twitching, numbness) = 5
- "Altered Cognitive Function" (impaired memory, disturbance in attention, disconnected thought) = 8

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For Neuropathic Pain?

Inhaled cannabis for chronic neuropathic pain: an individual patient data meta-analysis

J Pain. 2015 December ; 16(12): 1221–1232. doi:10.1016/j.jpain.2015.07.009.

Short term relief (>30% via VAS) of neuropathic pain with inhaled cannabis with NNT 5.6

Baynesian analysis of 5 RCTs, double blinded, placebo controlled, 178 patients in total

Similar in diabetic/trauma or HIV distal sensory neuropathy

Follow-up varied from several hours to **2 weeks**

Higher doses of THC associated with psychomimetic side effects

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For Pain in Multiple Sclerosis?

Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial

Dr John Zajicek, FRCP • Patrick Fox, MD • Hilary Sanders, BSc • David Wright, PhD • Jane Vickery, BSc • Prof Andrew Nunn, MSc • et al. Show all authors

THE LANCET
Volume 362, Issue 9395, 8 November 2003

630 patients treated with oral cannabis extract vs. synthetic THC vs placebo

Primary outcome = "Ashworth" spasticity score: no improvement

Secondary outcome = "Rivermead" mobility index: yes improvement

Benefit was less at 12 months compared to 3.5 months

No difference between cannabis extract vs. THC.

No long term data on side effects

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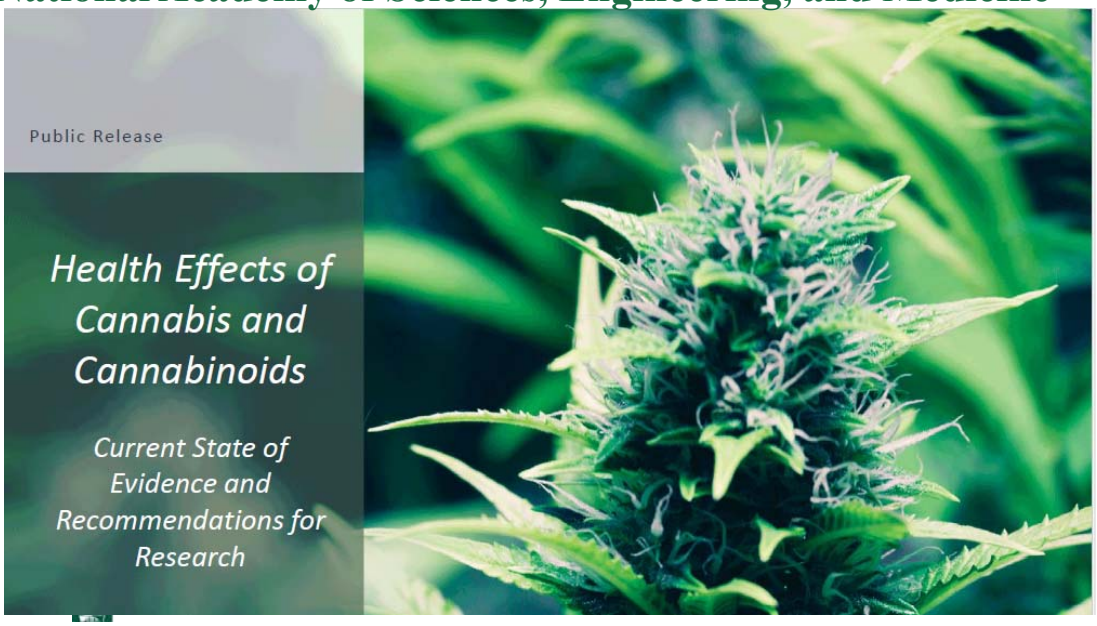
National Academy of Sciences, Engineering, and Medicine



Therapeutics

- In adults with chemotherapy induced nausea and vomiting, oral cannabinoids are effective antiemetics.
- In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms
- In adults with multiple sclerosis (MS) related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.
- For these conditions the effects of cannabinoids are modest; for all other conditions evaluated there is inadequate information to assess their effects.

Respiratory Disease

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

Cancer

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

Injury and Death

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

Psychosocial

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

Problem Cannabis Use

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

Mental Health

- There is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.
- In individuals with schizophrenia and other psychoses, a history of cannabis use may be linked to better performance on learning and memory tasks.
- Cannabis use does not appear to increase the likelihood of developing depression, anxiety, and posttraumatic stress disorder.
- For individuals diagnosed with bipolar disorders, near daily cannabis use may be linked to greater symptoms of bipolar disorder than non-users.
- Heavy cannabis users are more likely to report thoughts of suicide than non-users.
- Regular cannabis use is likely to increase the risk for developing social anxiety disorder.

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

Marcus A. Bachhuber, MD[1,2,3]; Brendan Saloner, PhD[3,4]; Chinazo O. Cunningham, MD, MS[5]; et al

JAMA Intern Med. 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005

Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D

Ashley C. Bradford[1] and W. David Bradford[2]

Health Aff (Millwood). 2016 Jul 1;35(7):1230-6. doi: 10.1377/hlthaff.2015.1661.

Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees

Hefei Wen, PhD[1]; Jason M. Hockenberry, PhD[2,3]

JAMA Intern Med. 2018;178(5):673-679. doi:10.1001/jamainternmed.2018.1007

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Ashley C. Bradford[1] and W. David Bradford[2]

Health Aff (Millwood). 2016 Jul 1;35(7):1230-6. doi: 10.1377/hlthaff.2015.1661.

- Between 2010 – 2013
- Looked at diagnoses for which cannabis *might* be used

	Condition category								
	Anxiety	**Depression**	**Glaucoma**	**Nausea**	**Pain**	**Psychosis**	**Seizures**	**Sleep disorders**	**Spasticity**
CLINICAL EVIDENCE OF MEDICAL MARIJUANA EFFECT ON CONDITIONS IN EACH CATEGORY									
Institute of Medicine (1999)[a]	Present	—[b]	Insufficient	Present	Present	—[b]	Insufficient	—[b]	Insufficient
Whiting et al. (2015)[c]	Very low	Very low	—[b]	Low	Moderate	Low	—[b]	Low or very low	Low to moderate

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Ashley C. Bradford[1] and W. David Bradford[2]

Health Aff (Millwood). 2016 Jul 1;35(7):1230-6. doi: 10.1377/hlthaff.2015.1661.

EXHIBIT 2

Daily doses filled per physician per year in states with and without a medical marijuana law

Condition category	Annual number of daily doses prescribed per physician in states: Without a medical marijuana law	With a medical marijuana law	Difference
Anxiety	11,220.29	10,113.77	1,106.51***
Depression	9,576.73	8,296.25	1,280.47***
Glaucoma	2,551.40	2,616.04	−64.64***
Nausea	10,067.92	9,040.22	1,027.70***
Pain	31,810.07	28,165.54	3,644.53***
Psychosis	11,421.46	10,298.60	1,122.86***
Seizures	9,398.60	8,028.74	1,369.85***
Sleep disorders	7,557.97	6,942.94	615.03***
Spasticity	2,067.82	1,645.43	422.38***

SOURCE Authors' analysis of data for 2010–13 from the disease-specific extracts in the Medicare Part D Prescription Drug Event Standard Analytic File. ***$p < 0.01$

Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees

JAMA Intern Med. 2018;178(5):673-679. doi:10.1001/jamainternmed.2018.1007

- Between 2011 – 2016
- States with medical marijuana and adult use marijuana
- Looked only at opioid prescribing rates, and only among Medicaid enrollees
- On average, about 5.8% lower

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CONTROLLED SUBSTANCES

Schedule	Symbol	Characteristics	Examples
I (C I)	C I	High abuse potential. May lead to severe dependence. NO ACCEPTED MEDICAL USE.	Heroin Marijuana Peyote
II (C II)	C II	High abuse potential. May lead to severe dependence.	Cocaine Morphine Codeine Methadone Amphetamine
III (C III)	C III	Abuse potential less than Schedules I and II. May lead to moderate dependence.	Drugs that are combinations of opiate and non-narcotic drugs, such as hydrocodone and acetaminophen (VICODIN)
IV (C IV)	C IV	Moderate abuse potential. May lead to limited dependence.	Alprazolam (XANAX) Zolpidem (AMBIEN) Phenobarbital (LUMINAL) Modafinil (PROVIGIL)
V (C V)	C V	Small abuse potential. May lead to limited dependence.	Cough medications with codeine, certain antidiarrheals.

Options for Treating Chronic Pain

1. Surgery
2. Physical Therapy
3. Medications
4. Injections
5. Complementary (Ayurveda, Reiki, Yoga, Acupuncture)
6. Not treating

QUESTIONS?