



Opioids and Cannabinoids: Delight or Dilemma for Chronic Pain Management

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Disclosures

- **Merrill Norton, PharmD, DPh, ICCDP-D, declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.**
- *Dr. Norton is the senior editor and a contributor to the book The Pharmacist's Guide to Opioid Use Disorders published by ASHP.*

Opioids for Chronic Pain Management Dilemma or Delight ???



COMBATING THE #OPIOIDCRISIS

115+
people DIE EVERY DAY
from opioid-related
drug overdoses.

NATIONAL INSTITUTE ON DRUG ABUSE



Dilemma or Delight : The Epidemic

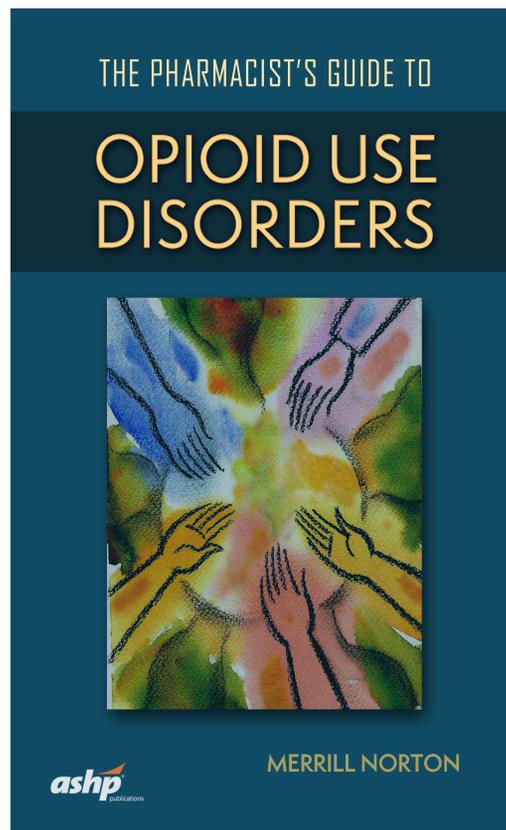
- Between 1999 and 2017, more than **700,000** people died from a drug overdose in the United States. The current epidemic of drug overdoses began in the 1990s with overdose deaths involving prescription opioids, driven by dramatic increases in prescribing of opioids for chronic pain. In 2010, rapid increases in overdose deaths involving heroin marked the second wave of opioid overdose deaths. The third wave began in 2013, when overdose deaths involving synthetic opioids, particularly those involving illicitly manufactured fentanyl, began to increase significantly. In addition to deaths, nonfatal overdoses from both prescription and illicit drugs are responsible for increasing emergency department visits and hospital admissions. In 2018, **73,000** additional deaths from opioid deaths were reported-the trend is moving higher each year-within 2 years it is estimated, that **1,000,000** Americans will have died from opioid overdose. **What can pharmacists and other healthcare professionals do to save America from this epidemic?**
- Centers for Disease Control and Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States. Surveillance Special Report 2. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Published August 31, 2018.

The Pharmacist's Guide To Opioid Use Disorders

ASHP Bookstore

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Ordering Info:
ashp.org/opioiddisorders



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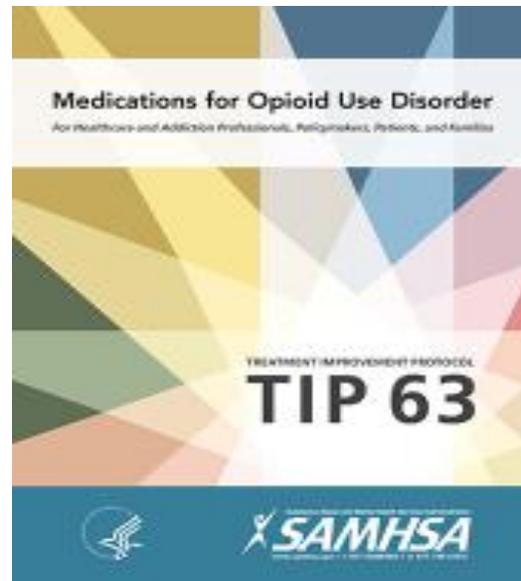


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Treatment Improvement Protocol 63 Medications for Opioid Use Disorder



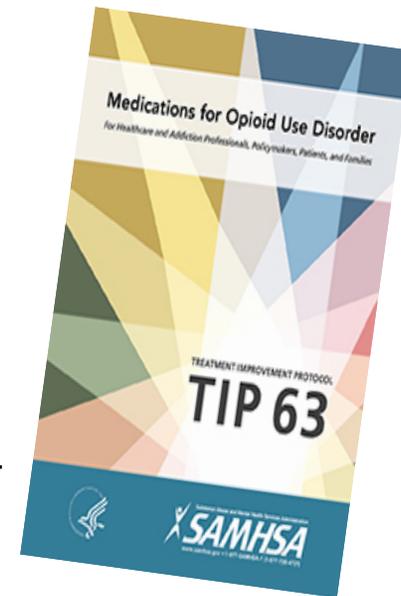
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www.samhsa.gov



Introduction

- The goal of treatment for opioid addiction or opioid use disorder (OUD) is remission leading to lasting recovery.
- This presentation summarizes TIP 63 content:
 - Food and Drug Administration (FDA)-approved medications for treating OUD
 - Other evidence-based care to support OUD recovery
- The Substance Abuse and Mental Health Services Administration's (SAMHSA) TIPs provide evidence-based, best-practice guidelines for the behavioral health field.

References for this presentation are available as a separate PDF.



Pain Relief

The fifth vital sign

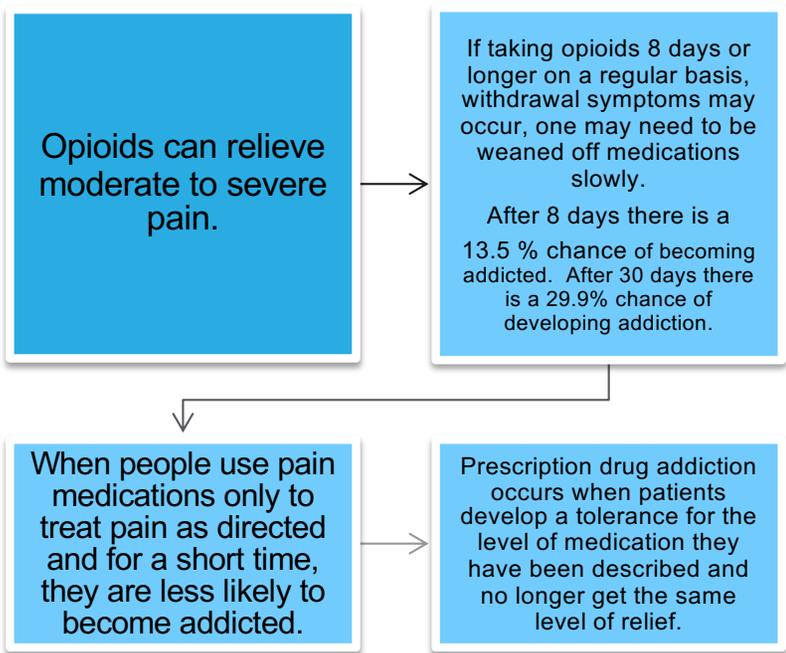
Pain control

Mind shift (Physicians and Patients)

Physicians trained to manage pain

The answer : prescription opioids

Pain Relief



Pain Management

Patients may not have the same expectations for relief as their physicians and may equate the term “painkillers” with the medication being able to take away all of their pain, while their doctor may be thinking in terms of pain management, which means bringing the pain to a level where they can function at a reasonable manner.



When expectations do not match, patients may take more of the pain medication than prescribed to get a higher level of relief and in turn develop a drug addiction issue.

Substance Use Disorders are Diseases

Substance use disorders are brain diseases mostly characterized by a person's inability to control his or her thoughts or intake of a substance.

A substance use disorder develops after a substance is repetitively consumed and the brain readjusts to its consistent presence.

Research shows that adaptations in neuronal functioning occur regardless of whether a person is taking legitimate medication for pain relief, consuming five beers as a first time drinker or injecting heroin on the streets.



So What's the Problem?

- **1 of 5 patients without non-cancer pain or pain related diagnoses are prescribed opioid pain medications.**
- **Nearly 3 million Americans abused or were dependent on prescription opioids in 2016.**
- **From 1999-2016 more than 630,000 people died from an overdose related to prescription opioids.**
- **As many as 1 in 4 patients prescribed opioids for chronic pain develops a opioid use disorder.**



So What's the Problem?

- Little is known about opioid prescribing among individuals who have survived cancer.
 - N=8601 Cancer Patients; N=8601 Non Cancer Patients
 - Cancer Survivorship Time Frames 5-10 years
 - The rate of opioid prescribing was 1.22 times higher among survivors than among their corresponding matched controls (adjusted relative rate, 1.22; 95% CI, 1.11-1.34).
 - This study demonstrates substantially higher opioid prescribing rates among cancer survivors, even long after attaining survivorship. This raises concerns about the diagnosis and management of chronic pain problems among survivors stemming from their cancer diagnosis or treatment.
-
- *Sutradhar,R. Lokku,A. Barbera,L. Cancer Survivorship and Opioid Prescribing Rate:A Population-Based Matched Cohort Study Among Individuals With and Without a History of Cancer; Cancer 2017;123:4286-93. VC 2017 American Cancer Society*

ASCO Recommendations for Cancer Patients

- Healthcare provider access to a choice of materials on prescribing education that is "evidence based and tailored by specialty"; No prescription limits that would "artificially impede access to medically necessary treatment for patients with cancer";
- **Patient education emphasizing safe use, storage, and disposal of prescription pain medication;**
- Allowances in prescription drug monitoring programs for providers who treat cancer related pain and "may prescribe relatively large numbers of opioids or provide multiple controlled drugs at relatively high doses";
- **Appropriate patient screening and assessment before and during opioid treatment, although use of compliance tools should not be mandated for all patients who receive opioids;**
- Use of abuse-deterrent -- or non-abuse deterrent -- formulations of prescription pain medication, as determined by clinical and patient-specific circumstances;
- **Rapid patient access to assessment, diagnosis, and treatment for opioid misuse, abuse, or addiction;**
- **Increased access to naloxone, "a life-saving medication in cases of opioid overdose"; and**
- Prescription "take-back" programs to decrease availability of unused or unwanted opioids, including readily available authorized collection sites for patients. National Take Back Day April 28, 2018
- For locations: www.deadiversion.usdoj.gov/drug_disposal/takeback/
- ASCO Policy Statement on Opioid Therapy: Protecting Access to Treatment for Cancer-Related Pain 2016

Prescription Opioid Use Often Leads to Heroin Use



4 out of 5 new heroin users
started misusing prescription
opioids¹

¹Hedegaard MD MSPH, Chen MS PhD, Warner PhD. Drug-Poisoning Deaths Involving Heroin: United States, 2000-2013. National Center for Health Statistics Data Brief. 2015:190:1-8.



Opioid Overdose

Overdose can occur immediately after drug ingestion OR could happen hours after drug ingestion

Overdose can last up to a couple of hours where the overdose victim experience respiratory depression

Fentanyl related overdoses tend to:

- Happen instantaneously
- Narrow window of time available to rescue the victim
- Require additional doses of naloxone to reverse effects of opioids
- Victims die from suffocation not the drug

Treatment

The goal of SUDS treatment is always to assist a client in stopping the compulsive use of drugs or alcohol and progress to living a normal, functional life.

SUDS creates a host of negative effects to the dependent client, his or her family and friends and society as a whole.

Research has shown that the most effective treatment regimen for opioid use disorders is a combination of medication assisted treatment, with cognitive behavioral therapy, and person centered therapy.

Medication Assisted Treatment (MAT)

- **The medication is only one aspect of treatment.**
- **The medication is intended to help prevent relapse while the addicted individual works to make lasting behavioral changes.**
- **A full treatment continuum should take place along with MAT; counseling and meetings are necessary for lasting recovery.**



Addressing Opioid Use Disorder in General Medical Settings

Screening, Assessment, and Referral

- **TIP 63 recommends universal OUD screening because of:**
 - The high prevalence of substance use disorders in primary care patients
 - The effectiveness of medications to treat OUD
- **Comprehensive assessment involves:**
 - Establishing the diagnosis and severity of OUD
 - Identifying any contraindicated medications
 - Indicating other medical, mental, and social issues to address
- **Referral to specialized care can provide patients with:**
 - Services comprehensive enough to meet their needs
 - The appropriate level of treatment

Practice Points for Opioid Management: Resources

- **CDC Guidelines Recommendations**
- **MAT Guidelines (TIP 63)**
- **ASAM Buprenorphine Guidelines**
- **ASAM National Practice Guidelines**
- **Centers for Disease Control and Prevention.**
- **2018 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States. Surveillance Special Report 2. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Published August 31, 2018.**

CDC Training Modules

- The CDC released eleven modules in the **Applying CDCs Guideline for Prescribing Opioids** interactive online training series for health care providers. In these self-paced modules, you will learn about opioid considerations in pregnancy, patient-centered communication practices, and approaches to shared, opioid decision-making. Each module includes clinical scenarios, knowledge feedback prompts and a resource library to help enhance learning.



The Two Tales of Marijuana: Medicine or Menace



Cannabinoids for Chronic Pain Management; Dilemma or Delight???



Oh Boy-Another Talk on Marijuana- Let's Get Stoned!!!!

- What are the benefits of marijuana?
- Is marijuana a medicine?
- Does marijuana have beneficial components to treat incurable chronic diseases?
- Should marijuana be legalized? If so, how should marijuana be regulated?
- List 5 adverse drug effects of THC.
- List 5 adverse drug effects of CBD.
- Should marijuana be a RX or OTC?
- At what age should some be allowed to purchase marijuana?
- What penalties should be in place for illegal use of marijuana?

Physician Prescribing Background

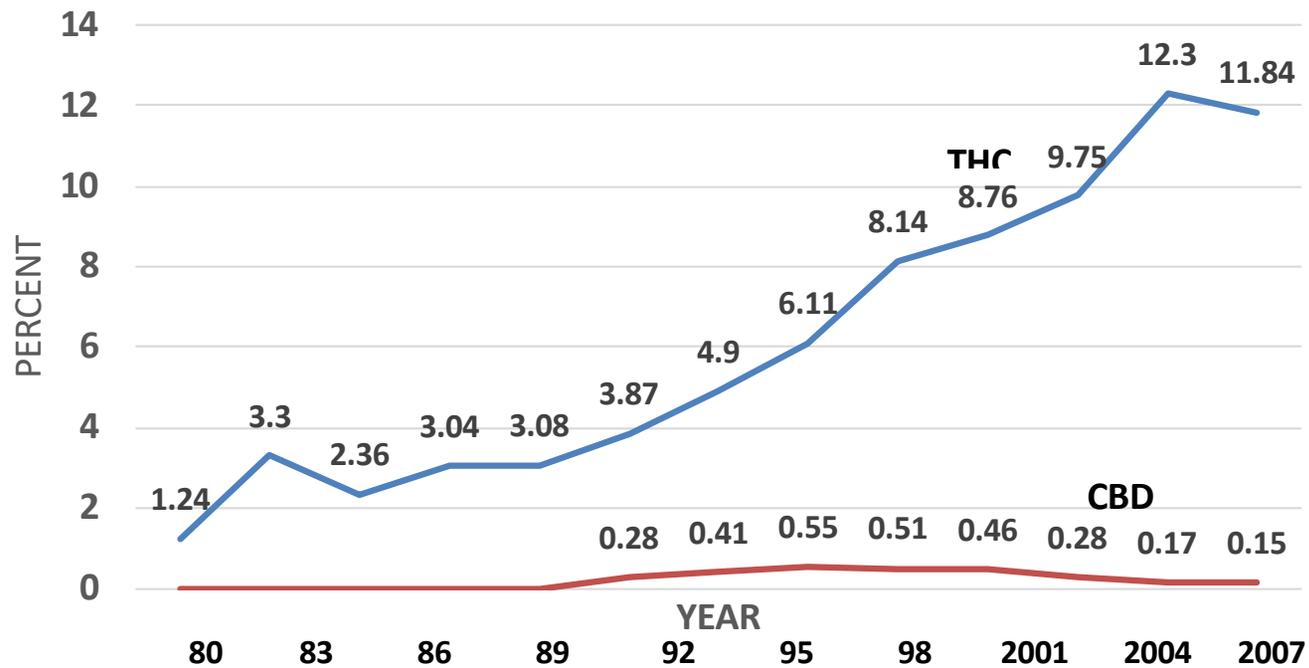
- ***The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research***
- 440 pages | 6 x 9 | PAPERBACK
- ISBN 978-0-309-45304-2 | DOI: 10.17226/24625
- Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda; Board on Population Health and Public Health Practice; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine

Cannabis and Cannabinoids

- Highly concentrated THC or cannabidiol (CBD) oil extracts are being illegally promoted as potential cancer cures. These oils have not been evaluated in any clinical trials for anticancer activity or safety.
- Because CBD is a potential inhibitor of certain cytochrome p450 enzymes, highly concentrated CBD oils used concurrently with conventional therapies that are metabolized by these enzymes could potentially increase toxicity or decrease the effectiveness of these therapies.
- *“Cannabis and Cannabinoids (PDQ®)—Health Professional Version was originally published by the National Cancer Institute.” (2018)*
- Cannabis and Cannabinoids (PDQ®)—Health Professional Version...
<https://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-...>
- 16



AVERAGE THC CONCENTRATIONS IN CANNABIS SEIZED BY DEA 1980 TO 2014



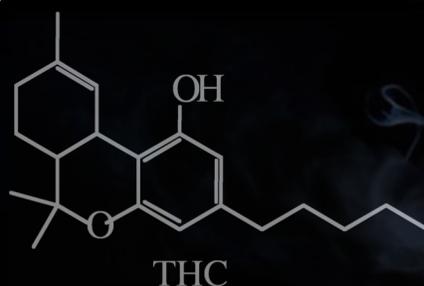
EISohly, et al. *Biological Psychiatry* 79:613 (2016)

EISohly, et al., *Journ of Forensic Sci* 45:24 (2000)

Chemical Constituents of Cannabis

Chemical classes

- Cannabinoids (66)
- Nitrogenous compounds (27)
- Amino acids(18)
- Proteins/ enzymes (11)
- Sugars (34)
- Hydrocarbons (50)
- Simple alcohols (7)
- Simple aldehydes (12)
- Simple ketones (13)
- Simple acids (21)
- Fatty acids (22)
- Simple esters/lactones (13)
- Steroids (11)
- Terpenes (20)
- Non-cannabinoid phenols (25)
- Flavoroids (21)
- Vitamins (1)
- Pigments (2)
- Elements (9)
- Total known compounds (483)**



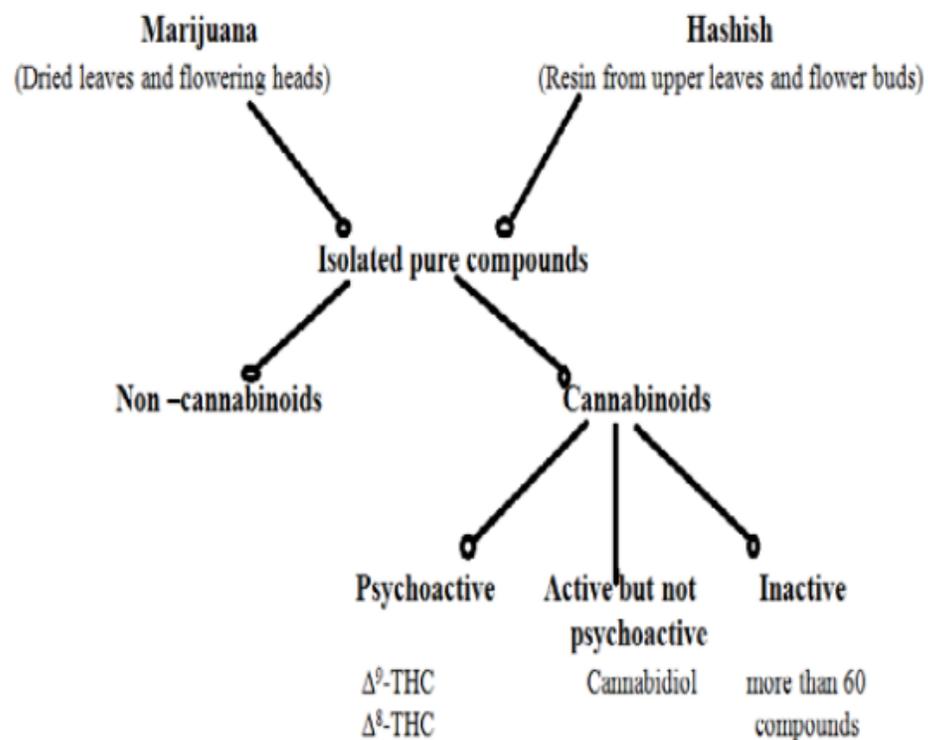
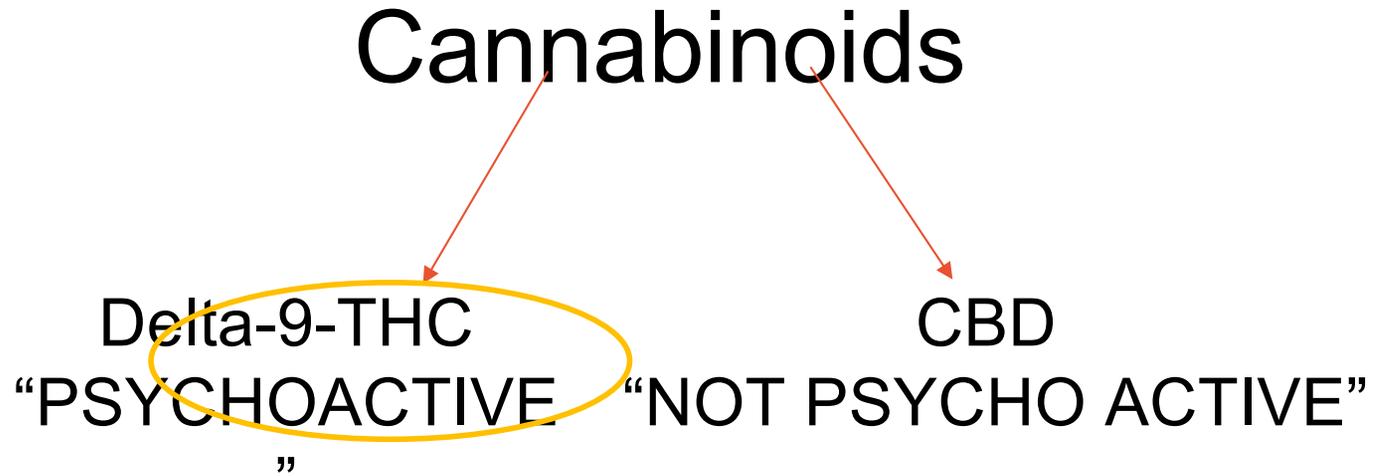


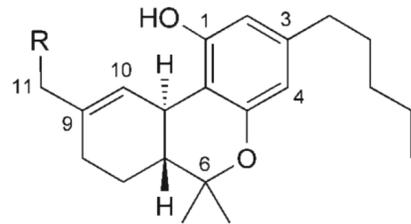
Figure 1. Chemical Components of Cannabis

Priyamvada Sharma, Pratima Murthy, M.M Srinivas Bharath. "Chemistry, Metabolism, and Toxicology of Cannabis: Clinical Implications". Iranian Journal of Psychiatry. October 1, 2012. pg. 149
<http://eds.b.ebscohost.com/eds/pdfviewer/pdfviewer?sid=14587b3e-f585-4dce-af43-007de0074755%40sessionmgr110&vid=16&hid=104>

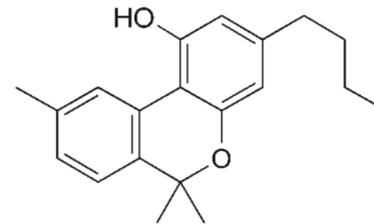
Psychoactive (Personal) vs Non-Psychoactive(Medical)



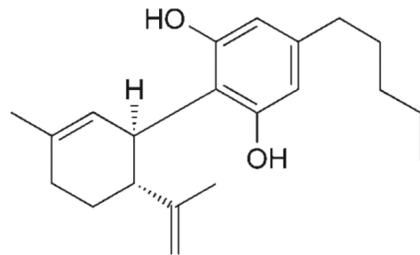
Cannabinoids



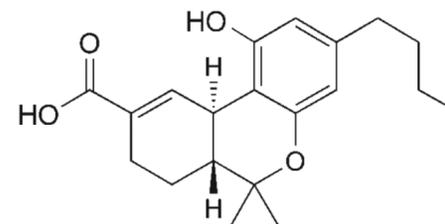
R = H Δ^9 -Tetrahydrocannabinol (THC)
 R = OH 11-Hydroxy variant (11-OH-THC)



Cannabinol (CBN)



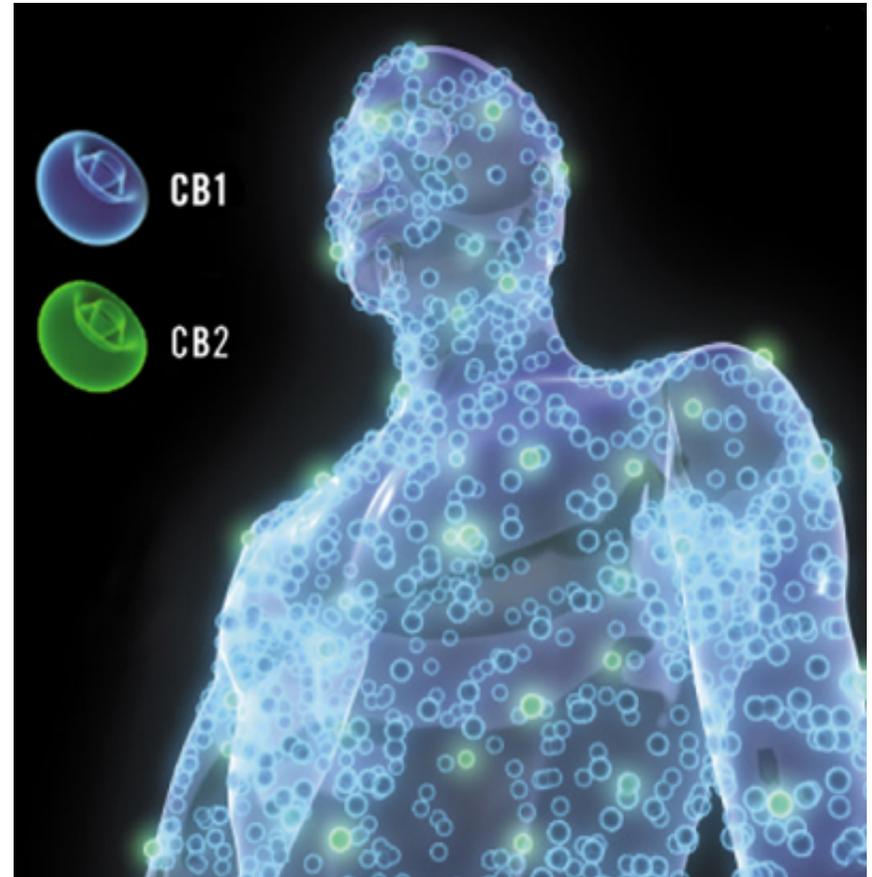
Cannabidiol (CBD)



'11-Nor-9-carboxy- Δ^9 -Tetrahydrocannabinol' (THC-COOH)

The Ubiquitous CB1

- Endogenous CBs are a major class of neuromodulators, acting through receptors, CB1 and CB2
- CB1 receptors are primarily located on CNS neurons
 - Levels exceed those of nearly all neurotransmitter receptors
- Exogenous CBs exert their effects by driving this innate system, often mimicking and enhancing its natural functions

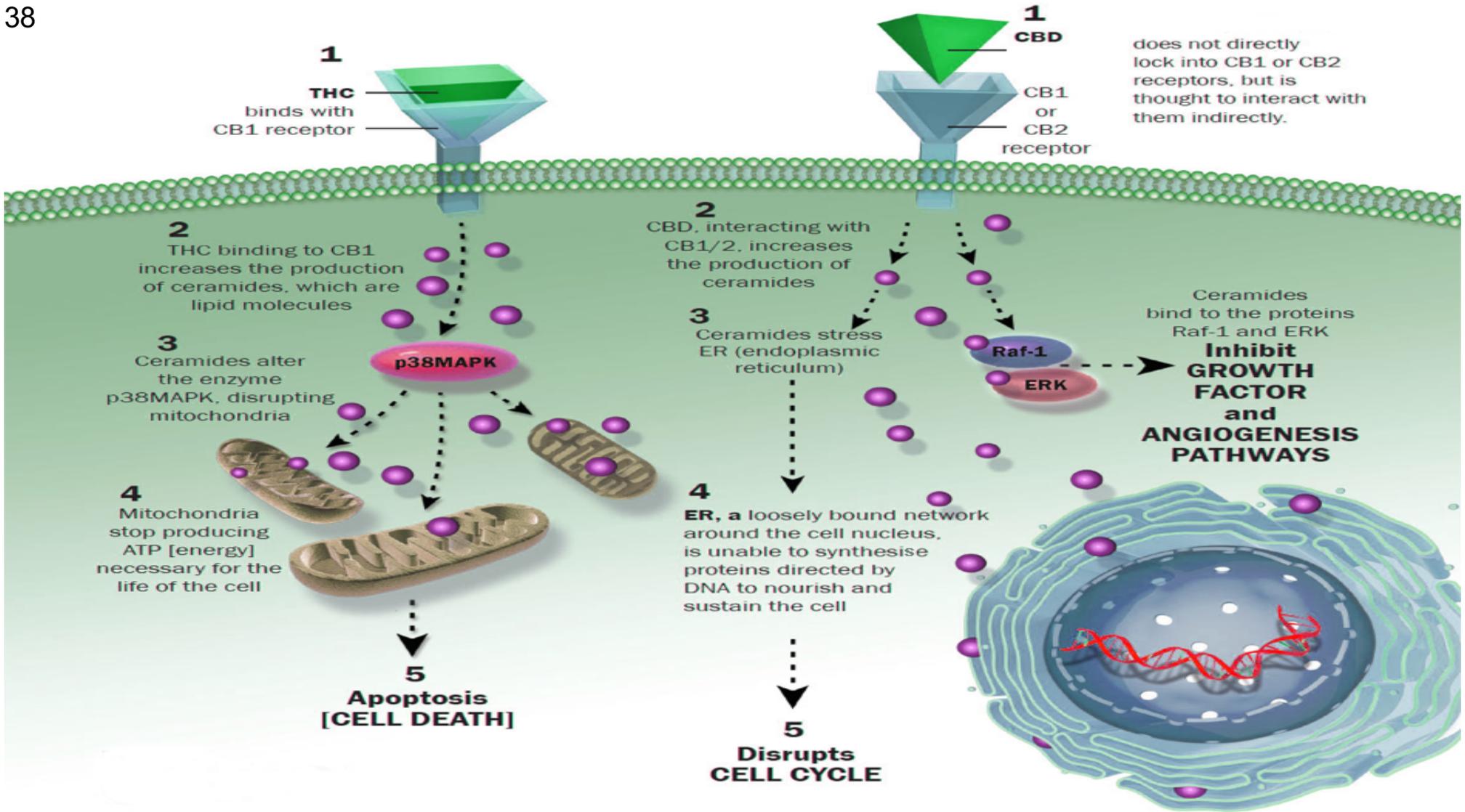


Cannabinoids

- THC :psychoactive, euphoria, increased reaction time, loss of memory/cognitive functioning decreases, clearance half-life of less than 30 minutes and is not detectable in urine
- CBN: Pain relief, Anti-insomnia, Promotes growth of bone cells, Antibacterial, Anti-inflammatory, Anti-convulsive, Appetite stimulant
- CBD: may modify THC effects, inhibits conversion of THC to 11-OH-THC (CYP450), formation of CBD from THC does not occur by heat from smoking nor by human metabolism, blocks anxiety and psychological side effects produced by THC intake
- THC-COOH: Lipid soluble component (metabolite), can be stored in fat cells for weeks to months, found in blood and urine, typically appears in the urine within 60 minutes, but can take as long as 4 hours, presence of the major THC-COOH >LOQ indicates exposure to THC within 3 days after a single use, to approximately 30 days in heavy chronic users

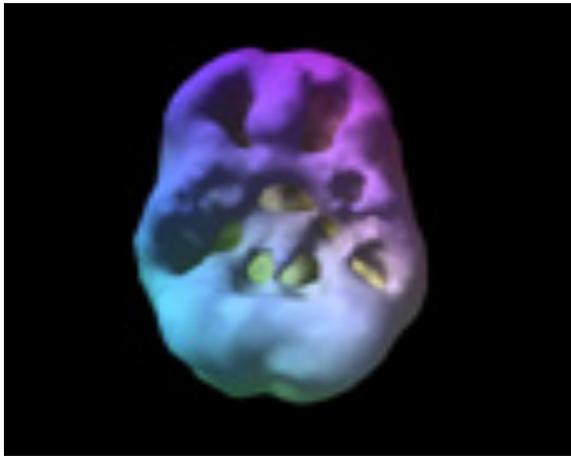
Marijuana Δ^9 -Tetrahydrocannabinol (THC), 2015, Mayo Clinic: Drugs of Abuse Testing,
<http://www.mayomedicallaboratories.com/test-info/drug-book/marijuana.html> (August 10, 2015)

Huestis, M. 2009, Human Cannabinoid Pharmacokinetics, *National Institute of Health: Chem Biodivers*, v. 4(8), p. 1770-1804.

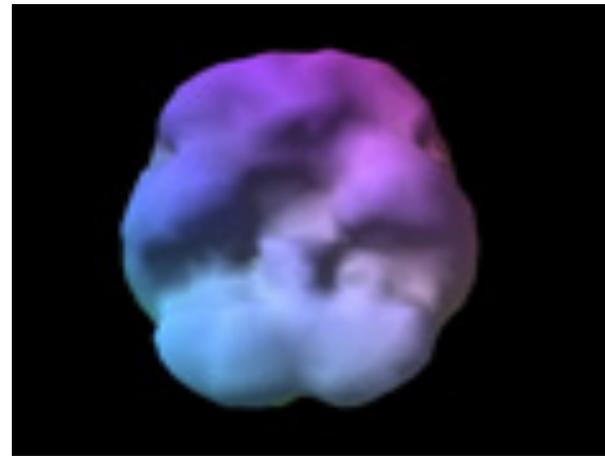


Impact of Cannabis Use Disorder

- MARIJUANA:

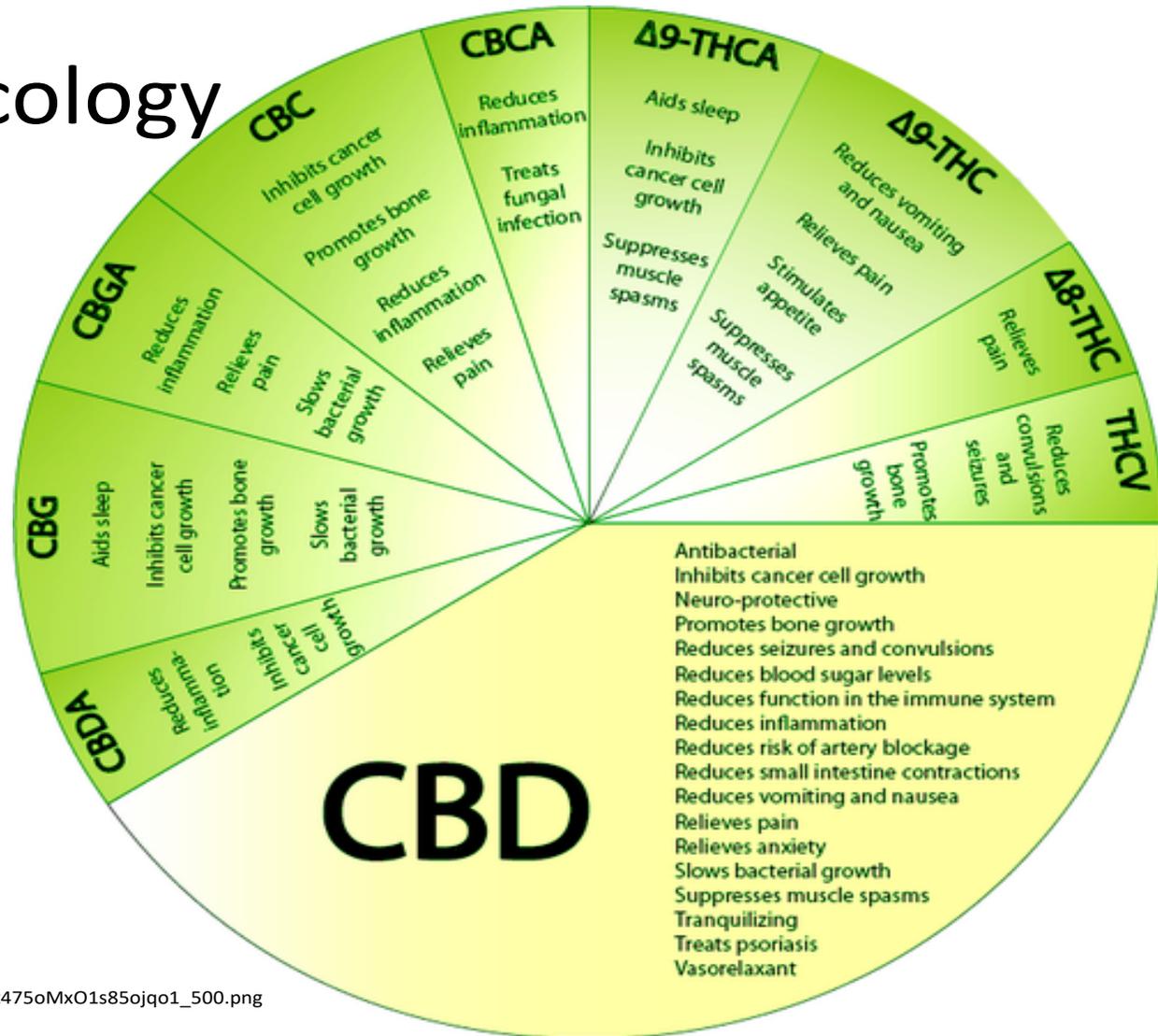


**16 year old
2 year history of daily use**



Normal

Pharmacology



https://cbbrothers.com/wp-content/uploads/2014/05/tumblr_mmt475oMxO1s85ojqo1_500.png

New Products for 2018



Latest Medical Cannabinols Efficacy Research

- Cannabis use was common in people with chronic non-cancer pain who had been prescribed opioids, but we found no evidence that cannabis use improved patient outcomes. People who used cannabis had greater pain and lower self-efficacy in managing pain, and there was no evidence that cannabis use reduced pain severity or interference or exerted an opioid-sparing effect. As cannabis use for medicinal purposes increases globally, it that large well designed clinical trials, which include people with complex comorbidities, are conducted to determine the efficacy of cannabis for chronic non-cancer pain.
- *Campbell, G et al: Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study; www.thelancet.com/public-health Vol 3 July 2018*

Latest Medical Cannabinols Efficacy Research

- **One meta-analysis** of 119 patients in 9 pain trials, 5 of which were exclusive to *cancer pain, found that tetrahydrocannabinol (THC) had an effect approximately equivalent to codeine, but dose-related and dose-limiting central nervous system (CNS) adverse events were common.*
- A more recent meta-analysis of *11 randomized controlled trials in chronic neuropathic pain demonstrated an insignificant overall change in pain scores, resulting in a weak recommendation for the use of cannabinoids.*
- **A meta-analysis** of the effects of cannabinoids on cancer pain in 43 randomized controlled trials revealed a beneficial effect in favor of cannabinoids, but patients were highly likely to experience significant CNS and gastrointestinal side effects.
- Cannabinoids for Cancer Pain - The ASCO Post; August 25, 2018

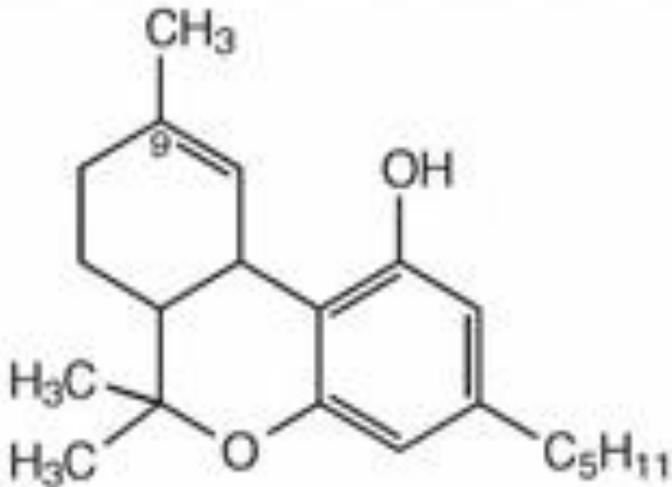
Latest Medical Cannabinols Efficacy Research-ADES

- Twenty-eight (13%) patients (N= 218) in the cannabis group reported at least 1 SAE, compared with 42 (19%) in the control group.
- Despite these limitations, this study improves our knowledge about the safety of medical cannabis. Caution should be exercised in interpreting these results for all medical cannabis use as patients in this study used a standardized, quality-controlled herbal cannabis product with a reliable THC potency of 12.5%.
- This study suggests that the AEs of medical cannabis are modest and comparable quantitatively and qualitatively with prescription cannabinoids. The results suggest that cannabis at average doses of 2.5 g/d in current cannabis users may be safe as part of a carefully monitored pain management program when conventional treatments have been considered medically inappropriate or inadequate.
- *Ware, M et al; Cannabis for the management of pain (COMPASS)*
<http://dx.doi.org/10.1016/j.jpain.2015.07.014>.

But What About the Current FDA Approved Cannabinols???

- Dronabinol(Marinol, Syndros) 1985, 2017
- Nabilone (Cesamet) 1985
- Cannabidiol (Epidiolex) 2018

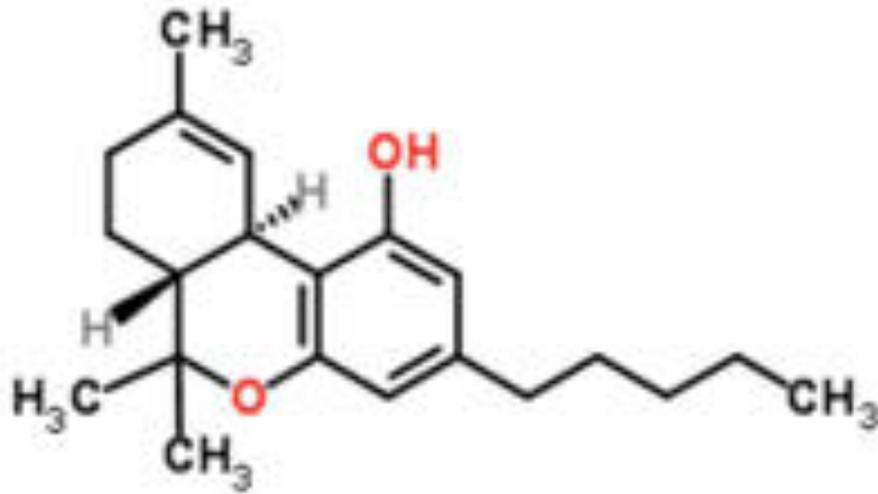
Dronabinol (Marinol)



$C_{21}H_{30}O_2$ (molecular weight = 314.47)

Marinol

- Dronabinol is a light yellow, sticky resinous oil formulated in sesame oil. It is insoluble in water and, therefore, only a fraction of the orally ingested compound reaches the patient's circulation. This amount is further reduced by the action of the liver, which recognizes dronabinol as a contaminant, and removes it from the bloodstream. As a result, researchers have estimated that only 10 to 20 percent of the dronabinol in each capsule actually reaches its target in the body.

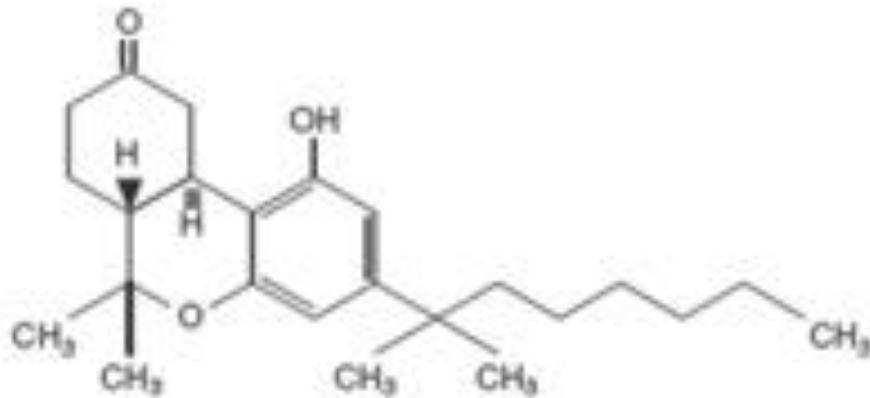


Syndros

Dronabinol (Syndros)

- Last year, the FDA approved a new liquid formulation of dronabinol. The new version of the drug is made by DPT Lakewood LLC for Insys Therapeutics and is marketed under the brand name **Syndros**.
- Indications are the same for Syndros as they are for Marinol: anorexia associated with weight loss in patients with AIDS, and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional treatment

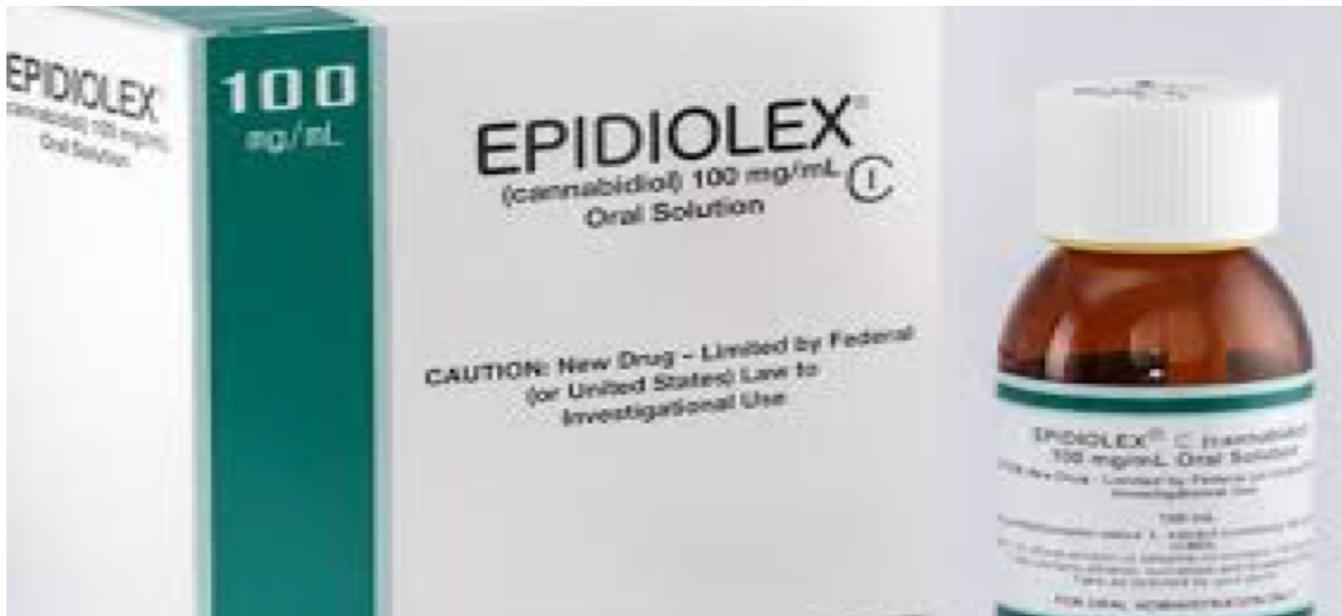
Nabilone (Cesamet)



Cesamet

- Cesamet (SES-uh-met) is the brand name for nabilone. Cesamet is a **purely man-made synthetic drug** that claims to activate the cannabinoid receptor CB1, which reduces proemetic signaling in the vomit center and thus inhibits nausea and vomiting. Cesamet claims it replicates the healing properties of delta-9-tetrahydrocannabinol (THC), but does not actually contain any of the constituents found in the *Cannabis* plant and thus, lacks the ability to tap into the entourage effect produced by whole plant cannabis medicines.
- Cesamet is classified as an antiemetic. Antiemetics are medicines that help prevent or treat chemotherapy-induced nausea and vomiting (CINV). Cesamet is to be prescribed to people who continue to experience these symptoms after trying other traditional medications, specifically antiemetics, to find relief.

Epidiolex (Cannabidiol 100mg/ml Oral Solution)



Adverse Drug Effects(ADES)



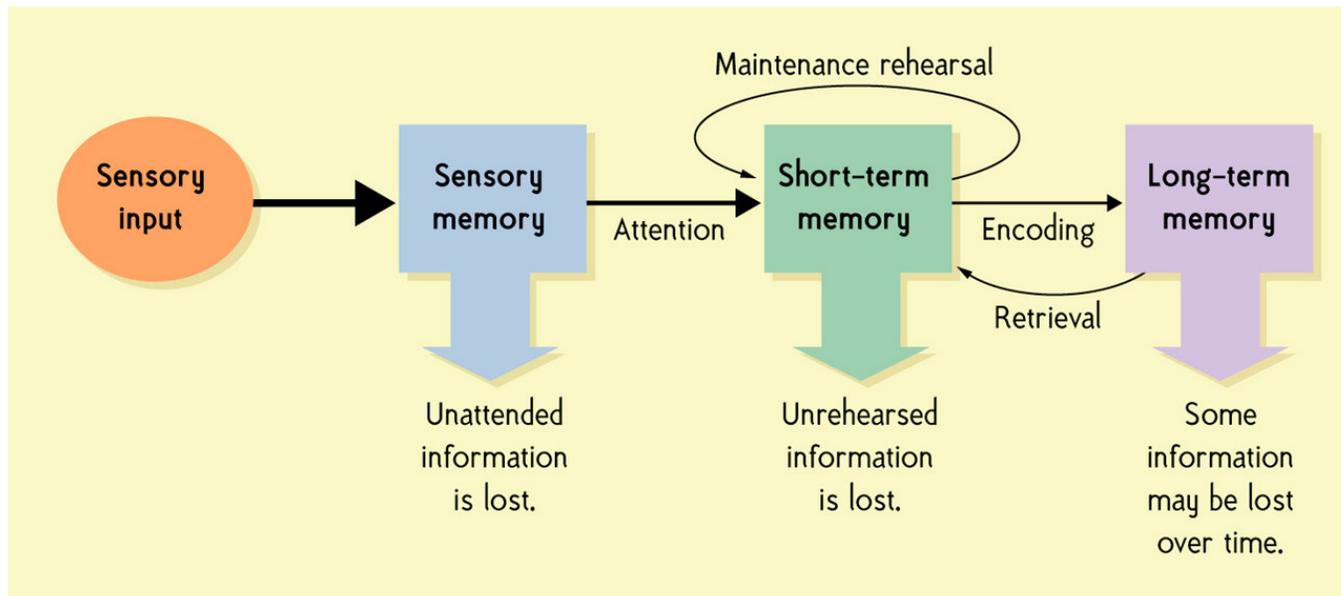
Memory

- Memory
 - persistence of learning over time via the storage and retrieval of information

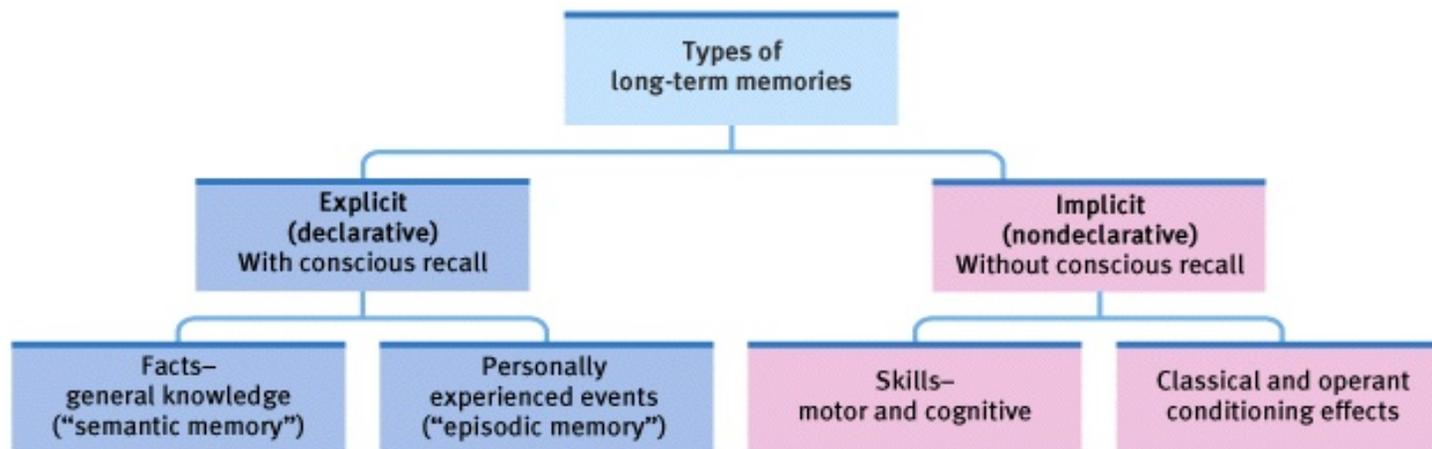
Memory

- Encoding
 - the processing of information into the memory system
- Storage
 - the retention of encoded information over time
- Retrieval
 - process of getting information out of memory

The Modal Memory System



Stage 3: Long Term Memory



Explicit Memory

- Explicit memory involves the processes used to remember specific information which can be declared
- Episodic memory is personal
- Semantic memory involves knowledge of facts

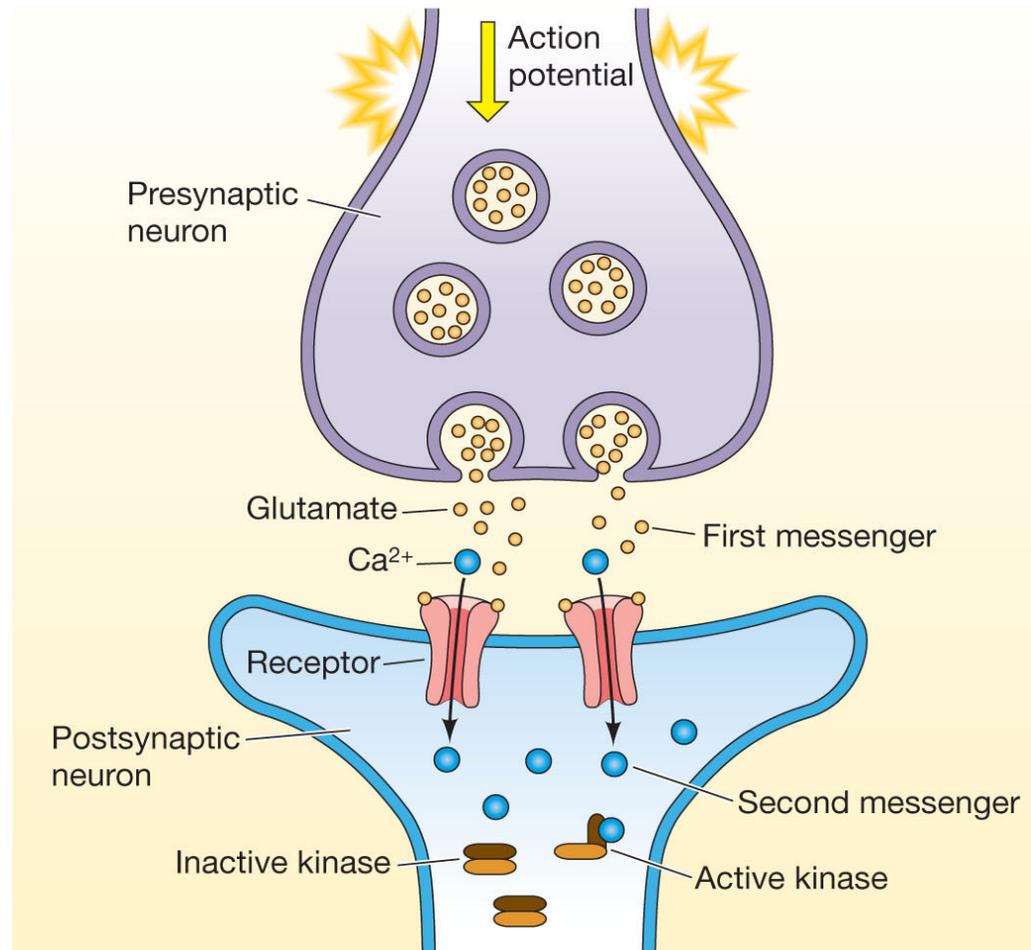
Implicit Memory

- Implicit memory is the pervasive process by which people show without awareness that they are remembering something
- Implicit memory does not require attention and is automatic
- Consider “procedural memory”
- Repetition priming

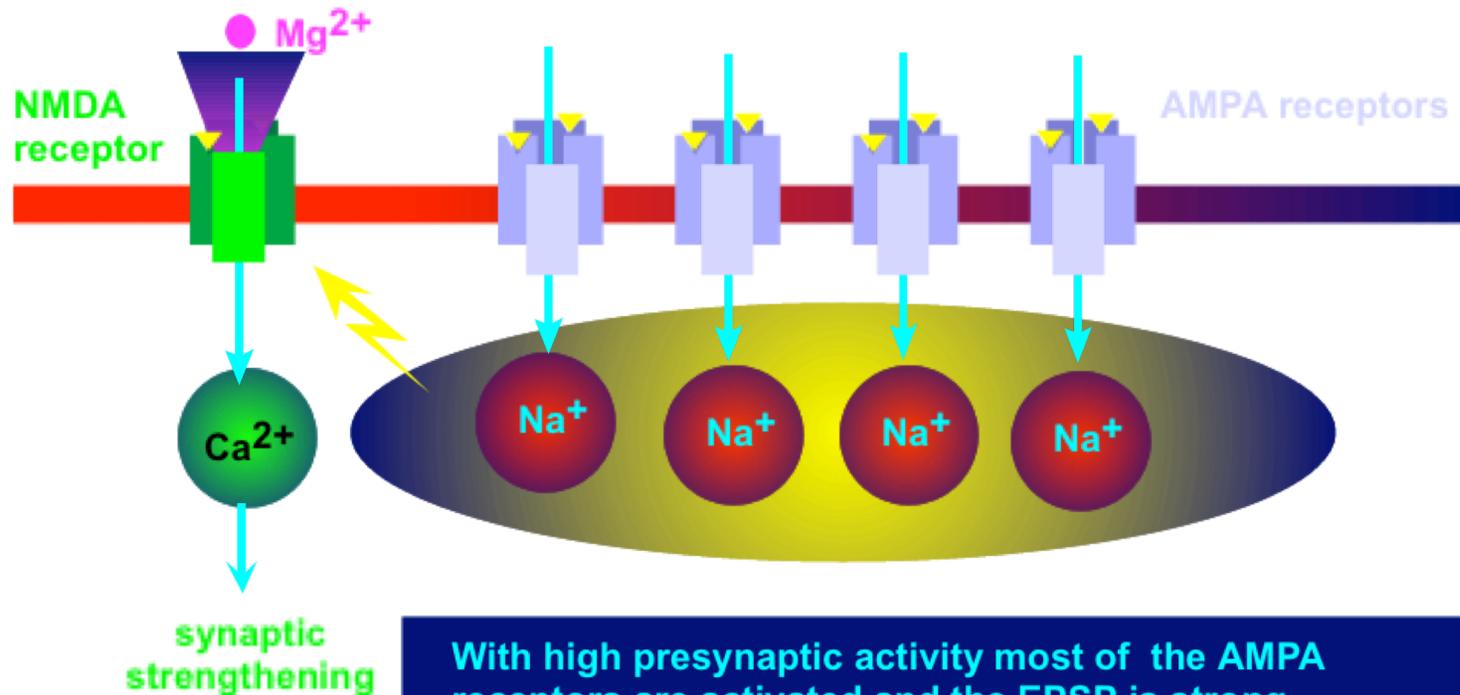
Retrieval

- **Recall**
 - retrieve information learned earlier
- **Recognition**
 - identify items previously learned

Figure 3.1 First messengers carry information between neurons; second messengers carry the signal into the neuron



Neurobiology of Learning and Memory, Figure 3.1



With high presynaptic activity most of the AMPA receptors are activated and the EPSP is strong.

The strong EPSP (or back-propagated action potential) lifts the Mg²⁺ block of the NMDA receptor.

The Ca²⁺ signal ultimately leads to synaptic strengthening.



Canadian Study on ADEs

- **Canadian Medical Association**
- **Products include Sativex, Marinol, Nabilone, and leaf Marijuana**
- **321 articles**
- **N= 4779 Adverse events reports (4515 reported as non serious) and 164 reported as serious**
- **15 deaths reported**
- **Not all studies reported ADEs**
- **Serious ADEs include respiratory, renal, cardiac, infectious disease**

Opioids and Cannabinoids: Delight or Dilemma for Chronic Pain Management Summary

- Use of opioids for chronic pain syndromes are NOT recommended unless VERY close supervision is applied to patient care;
- Increased dosages of opioids for cancer survivors is on the rise-close supervision required;
- At the present time, the latest medical studies indicate that neither THC or CBD preparations provide adequate pain reduction for severe chronic non cancer or cancer pain;
- Much more research is required before an appropriate substitution of medical cannabinoids for opioids;
- Most experts will support the placebo effect of cannabinoids in place of opioids.

Questions????

