

Medical Marijuana and Pain Management: What We Need to Know

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Objectives

- To understand the physiology of cannabis
- To review the medical criteria for the use of cannabis
- To understand the side effects and controversies associated with the medical use of cannabis

True or False

Is it true that a recent JAMA article notes that in states that legalized weed, the number of opioid prescriptions and the daily dose of opioids went down?

Is it true that in states with medical marijuana laws noted 25% fewer deaths from opioid overdoses?

(Where Marijuana is Legal, Opioid Prescriptions Fall, Kate Sheridan. April 5, 2018. Scientific American)

Current Perspectives

- Medicare filled 14% fewer prescriptions for opioids after medical marijuana laws were passed in their states.
 - (Bradford AC, etal JAMA InternMed. 2018 Apr2.doi 10.1001/jamainternmed.2018.0266)
- Medicaid enrollees filled 40% fewer opioid prescriptions per 1000 people each year after their sates massed any law making cannabiss accessible...with greater drops seen in states that legalized both medical and recreational marijuana.
 - (Vyas MB, etal Nurs Outlook. 2018 Jan-Feb;66(1):56-65)

State Statutes

- 28 states: AK, AR, AZ, CA, CO, CT, DE, FL, HI, IL, ME, MD, MA, MI, MN, MO, NV, NH, NJ, NM, NY, ND, OH, OR, PA, RI, VT, WA, and DC. CA-1966, ME-199/2010
- 16 states with CBD only statutes: AL, DE, FL, GA, IO, KY, MS, MI, NC, OK, SC, TN, TX, UT, VA, WI
- 8 States with recreational marijuana : AK, CA, CO, Mam ME, NV, OR, DC
- (www.procon.org)

Medical Use of Cannabis in Europe

- Legal or decriminalized in 21 countries:
Austria, Belgium, Croatia, Czech Republic,
Estonia, Finland, France, Germany, Italy,
Macedonia, Malta, the Netherlands, Portugal,
Romania, Russia, Ukraine, United Kingdom
(Ireland pending)

Medical Indications in 1999

- Persistent nausea to treat cancer. , vomiting, wasting syndrome or loss of appetite as a result of AIDS, chemo and radiation therapy
- Heightened intraocular pressure as a result of glaucoma
- Seizures associated with a chronic debilitating disease e.g. epilepsy
- Persistent muscle spasm associated with a chronic debilitating disease e.g. Multiple sclerosis.

Referendum November 2009

- Establishment of 8 dispensaries in Maine
- Establishment of a bona-fide doctor-patient relationship
- Expanded Medical indications: Hepatitis C, Crohn's disease, Agitation from Alzheimer's dementia, ALS, Nail Patella Syndrome AND INTRACTABLE PAIN of greater than 6 months duration

Before 2009....

- Prior to 2009 muscle spasms e.g. MS and injuries e.g. dystonia, back spasms; and nausea, vomiting, cachexia from cancer were the most common requests.
- One request for glaucoma and seizures disorder.

Requests since November 2009

- Chronic pain: usually trauma/ injury to head, back, neck: fibromyalgia, chronic headache, advanced arthritis.
- Crohn's disease and other gastrointestinal disorders with persistent nausea, cachexia, anorexia, ulcerative colitis.
- Muscle spasm due too numerous neurological conditions: MS, Freidrich's ataxia, dystonia, Parkinson's disease.

Historical medical references

- 3rd-8th cent BC used for phlegm, catarrh, and diarrhea, aphrodisiac and pain, the fumes of burning hemp for anesthesia
- William O'Shaughnessy in 1839 published a review Sanskrit and Unami sources and reintroduced cannabis for cholera, rheumatic disease, delirium tremens, infantile convulsions.

History in the US

- Classified in 1851 as a legitimate medical compound in the US Pharmacopeia and Dispensary, then removed in 1942
- Criminalized in 1937 against the advice of the AMA and pharmaceutical industry
- Banned in the absence of scientific evidence and associated with the “reefer madness campaign”
- Illegal under the Controlled Substance Act of 1970
- DEA classified it as a Schedule 1 drug

A Few Comments about Physiology

- 400 different chemical compounds in a typical marijuana plant/bud including THC (9- and tetrahydrocannabinol) and CBD (cannabidiol) these are terpenophenolic compounds.
- A group of terpenes, aromatic compounds that impart flavor and the characteristic odor comprise the whole plant effect is referred to as the “entourage effect” e.g. d-linalool (lavendar) anxiolytic, p-myrene (hops) antispasmodic, alpha-pinene (pine needles) anti-inflammatory

Cannabinoid receptors

- ENDO-cannabinoid (EC) receptors (Rc) are found in the human body on many types of cell membranes. Discovered in 1990.
- Endogenous forms: anandamide and 2-arachidonoylglycerol
- THC and CBD in plants
- Synthetic forms: dronabinol (Marinol, synthetic THC, schedule 3) nabiximol (Sativex, THC and CBD pure plant extracts) in stage 3 trials

Receptors

- THC is mediated through CB1 Rc which mediates feelings of euphoria, altered sense of time, analgesia, increased appetite, lowers anxiety. They are widely distributed in the central nervous system
- CBD is mediated through CB2 Rc which affect the immune system, gut function, brain function, and vascular activity.
- There are no CB Rc's in the brainstem & heart

Available forms of Cannabis

Dried herb used to smoke or vaporize

Edibles: cookies, candies, butter or ghee

Fresh green tips of plant: used in cooking to spaghetti sauce or used as a tea.

Liquid extract: glycerin/water based contain THC and CBD; alcohol or tincture contains only CBD

Topical salves

Concentrated oils: CO2 or butane extractions

Management of Chronic Pain

- Cannabinoids act synergistically with opioids and act as opioid sparing agents allowing for lower doses and fewer side effects from chronic opioid therapy.
- (Elikottil J etal J Opioid Manag. 2009 Nov-Dec;5(6); 341-57)

Synergy with Opiate Use

- Medical cannabis use was associated within opioid use a 64% decrease in opioid use (n=118), decreased number of side effects of medications, improved quality of life (45%)
- Cross-sectional retrospective survey of 244 medical cannabis patients with chronic pain. Patrons at a medical cannabis dispensary in MI

(Boehnke KF, et al J Pain 2016 Mar 18. pii: s1526-5900 (16) 00567-8)

Different Types of Pain

- Various forms of medical cannabis have provided mostly positive response for patients with different types of pain: neuropathic, chronic, post-operative, fibromyalgia, rheumatoid arthritis, multiple sclerosis and cancer.
- (Borgelt, LM etal The Pharmacologic and Clinical Effects of Medical Cannabis. Pharmacotherapy. Vol. 33, no 2, 2013195-209)

Opioid and Cannabinoid Interactions

- Recent studies indicate that opioid and cannabinoid anti-nociception (Pain decrease) may have additive or even synergistic anti-nociceptive effects.
- Clinically this may enhance analgesic effects with lower doses and consequently fewer undesirable side effects.
- (Deroches J, etal Curr Drug Targets 2010 Apr; 11(4): 462-73)

Synergy: Cannabis and Opioids

- The combination of THC in low, non-psychoactive doses with opioids has a synergistic effect and reduces the opioid tolerance effects.
 - (Karst M, Expert Opin Investig Drugs. 2009 Feb; 18(2): 125-33)
- Synergistic interactions between cannabinoid and opioid receptors show potential reduction in drug-seeking behavior and opiate sparing effects. (Leung L, etal J Am Board Fam Med. 2011 Jul-Aug; 24(4): 452-62)

Side Effects

- Dry mouth (xerostomia), large doses may exacerbate vomiting, tachycardia, hypotension or hypertension, syncope, palpitations.
- May effect motor coordination, reaction time, and visual perceptions
- May exacerbate panic attacks, hallucinations, flashbacks, depression and other emotional disturbances.
- Chronic use may cause laryngitis, bronchitis, sexual dysfunction, abnormal menstruation

Interactions with Herbs and Supplements

- Sedation may occur with concomitant use of 5-HTP, calamus, California poppy, catnip, hops, Jamacian dogwood, scullcap, valerian, yerba mansa, among others.

Interactions with Pharmaceuticals

- Competes with barbiturate metabolism and increase drug levels.
- Might exacerbate CNS depressants
- Once case of hypomania reported with disulfiram (antabuse) and fluoxetine (prozac)
- May increase the metabolism of theophylline
- Using more than 2 oz week may increase INR (anti-coagulation with warfarin or coumadin)

Mental Health Effects: PTSD

- Preliminary studies in humans suggest that treatment with cannabis may decrease PTSD symptoms including sleep quality, frequency of nightmares and hyper-arousal.
- Moreover, cannabis administered after exposure to a traumatic event were found to prevent the development of the PTSD-like phenotype.
- (Mizarchi Zer-Aviv t, etal Cannabinoids and post-traumatic stress disorderL clinical and preclinical evidence for treatment and prevention. Behav Pharmacol. 2016 Oct 27(7);561-9)

Mental Health: Panic Disorder

- Studies suggest an anxiolytic effect of CBD on healthy volunteers with social anxiety disorder.
 - (Schier AR, etal Cannabidiol, a cannabis sativa constituent, as an anxiolytic drug. Rec Bras Psiquiatr. 2012 June; 34 Supple 1: S104-10)
- Human studies clearly suggest an anxiolytic like effect on CBD in healthy.
 - (Soares VP, etal. Evidence of the anti-panic Actions of Cannabidiol. Curr Neuropharmacol. 2017;15(2):291-299)

Cannabidiol in Psychiatry

- Limited benefit in bipolar disorder and major depression
 - (Khoury JM, etal Is there a role for cannabidiol in psychiatry. World J Biol Psychiatry. 2017 Jan 23:1-34)
- Cannabidiol alleviates anxiety in paradigms assessing innate fear. 1) depresses fear expression acutely. 2) disrupts fear consolidation. 3) enhances extinction.
 - (Jurkus R, etal. Cannabidiol regulation of learned behavior: implications for treating anxiety-related disorders. Front Pharmacol. 2016 Nov 24,7:454)

More on Mental Health

- CBD reduces anxiety through 5-HTP (precursor to serotonin)
- CBD reduces fear expression acutely and disrupts fear memory consolidation , and enhances fear extinction.
- (LeeJL, etal. Cannabidiol expression regulation of emotion and emotinal memory processing: relevance for treating anxiety-related and substance abuse disorders. Br J Pharmacol 2017 Mar 7)

Incidence of Schizophrenia in Adolescents

- Growing concern that “synaptic pruning” is influenced by endocannabinoids (Freund TF, etal Role of endogenous cannabinoids in synpatic signaling. *Physiol Rev* 2003;83:1017-66)
- Continuous use of cannabis in schizophrenia is associated with more sever psychosis. (Foti DJ, etal Cannabis Use and the course of schizophrenia: 10-year follow-up study) *Am J Psychiatry* 2010;167: 978093)
- In order to delineate potential neurobiological and neurochemical mechanisms that underlie the effects of cannabis in psychotic disorders, more research is needed. (Sami MB, etal. *J Psychopharmacol.* 2018 Mar 1: 2698811187606620)

CBD and Psychosis

- CBD appears to have pharmacological profile similar to that of atypical anti-psychotics .(Zuardi AW, etal Curr Pharm Des. 2012;18(32);5131-40)
- CBD may counter the effects of THC that can cause symptoms of schizophrenia. (Manseau MW, etal. Neurotherapeutics. 2015 Oct;12(4): 816-24)

Cannabis Use Disorder

- Clinically significant impairment or distress as manifested by at least 2 of the following occurring within a 12-month period.
- Cannabis used more than intended.
- Persistent desire to use or inability to cut down on use
- Spending a great deal of time seeking, using and recovering from cannabis use.
- Craving, strong desire or urge to use.

Cannabis Use Disorder

- Failure to fulfill obligations at work, school or home.
- Persistent use despite recurrent social or interpersonal problems
- Giving up important social, occupational or recreational activities
- Recurrent use of physically hazardous situations

More....

- Persistent use despite the knowledge of the physical or psychological problems created by use
- Tolerance either increased use or diminished effect.
- Withdrawal syndrome or use to avoid
- (Source: DSM-5)d

A Few Resources

- Medical Cannabis Primer: For Health Care Professionals by Laura Bultman, MD and Kyle Kingsley, MD
- Medical Cannabis by George L Smith, MD
- Cannabis Pharmacy by Michael Backes
- The Pharmacologic and Clinical Effects of Medical Cannabis. Borgelt, LM. Etal. Pharmacotherapy 2013;33(2):195-209.
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