Integrating Medical Marijuana into a Pain Practice

Introduction

- Zeeshan Tayeb, MD
- No Disclosures

- Pain Specialists of Cincinnati

Pain Specialists of Cincinnati

Objectives/Overview

- A Brief History of Medical Cannabis
- Endocannabinoid Physiology, Phytocannabinoid Pharmacology
- Recommending Cannabis as a Medicine: Dosing and Delivery
- Cannabis Toxicology, Side Effects, and Addiction Potential
- Clinical Indications: PAIN – to integrate or not, that is the question
- Legal Considerations

Is it the perfect fit?

Best thing since sliced bread?

Now what about some…

- Magical Butter
- Cannabis Cures
- End the Drug War
- Medical Cannabis

Peanut butter and … where's the jelly?

Is the grass (weed) greener on the other side?

History of Marijuana

- 6000 BC – Cannabis seeds used as food in China
- 4000 BC – Textiles made of hemp in China
- 2727 BC – first recorded medicinal use in Chinese Pharmacopoeia
- 1400 BC to AD – trade moves product through India, Mediterranean countries, Europe – numerous medicinal uses reported

History of Marijuana

- Introduced to North America in 1600s by Puritans – Hemp for ropes, sails, clothing; cannabis a common ingredient in medicines, sold openly in pharmacies
- 1937 – Marijuana Tax Act – transfer of cannabis illegal throughout US except for medicinal and industrial use, expensive excise tax and detailed logs required
- 1969 – found to be unconstitutional since it violated 5th Amendment privilege against self-recrimination

History continued

- 1970 – Controlled Substance Act – classified cannabis as having:
  - High abuse potential
  - No medical use
  - Not safe to use under medical supervision
- 1975 – FDA establishes Compassionate Use Program for Medical Marijuana – Glaucoma, Multiple Sclerosis, Cancer
- 1986 – Dronabinol placed into Schedule II by DEA
- 2003 – Canada – 1st country in world to offer medical marijuana to patients

Indications

- Dronabinol (Marinol) and nabilone (Cesamet) indicated for chemotherapy-induced nausea and vomiting
- Dronabinol (Marinol) approved for HIV-associated anorexia
- Sativex (oromucosal spray) conditionally approved for neuropathic pain in multiple sclerosis and cancer pain
- Herbal smoked marijuana – found to be safe and effective for HIV-associated disorders

“Smoking” questions…

Measure 91 vs Medical Marijuana?

Is it legal?

Is it beneficial?

SAFE?

How does it work?

Drug interactions?

Monitor?

How to quit using?

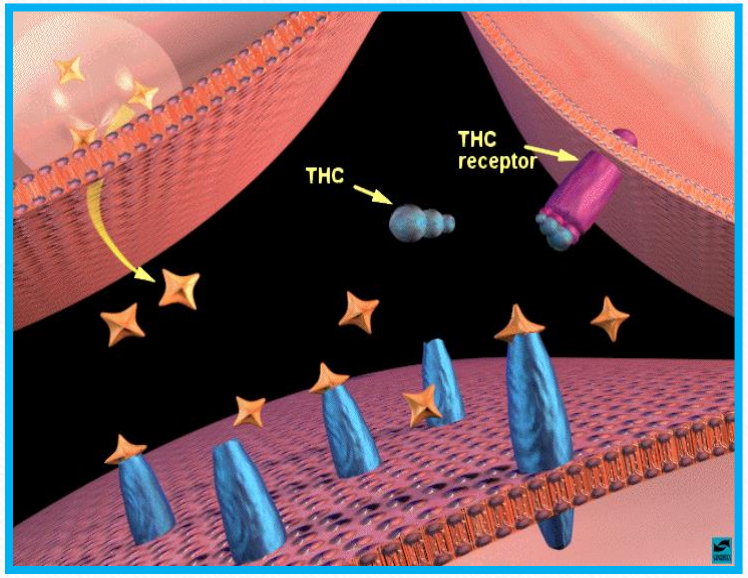
How do I talk to patients about it?

Marijuana: What is it?

- Dry, shredded mix of leaves, flowers, stems, and seeds, usually from *Cannabis sativa* or *Cannabis indica* plant
- Both are common subspecies of the hemp plant, which is common throughout the world
- Contains over 4-500 chemical compounds
- Common names: grass, weed, pot, reefer, Mary Jane, ganja

SOURCE: SAMHSA, 2012 (reference list).

Marijuana: How Does it Work?



- Contains over 60 cannabinoids: main active chemical is Δ-9-tetrahydrocannabinol (THC)
- Stimulates "high" by triggering receptors in parts of brain that influence pleasure, memory, thinking, concentration, coordination
- THC's molecular structure is similar to that of neurotransmitters that affect cannabinoid receptors (affect pain, appetite, vomiting reflex)
- Effects generally last 1-4 hours

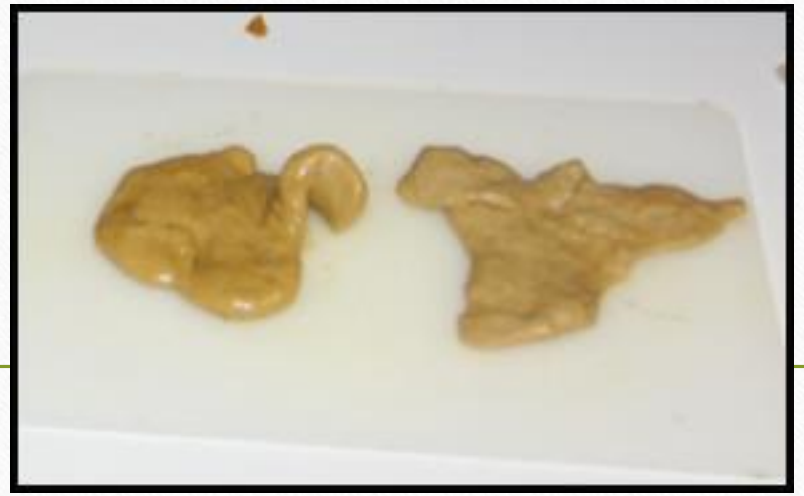
SOURCES: Eddy, 2010; NIDA, 2012a, 2012b (reference list).

Cannabis Basics

- Chemistry
  - Cannabinoids / Receptors
  - Smoked
    - Quick effect
    - Peaks at 20 min. Lasts 1-2 hours
  - Eaten
    - Onset 1-2 hours
    - Effects last for 3-4 hours

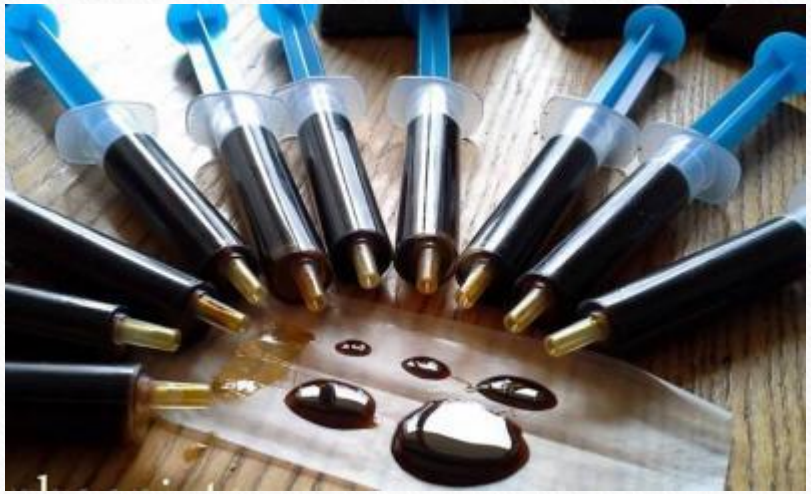
Cannabis "raw materials"

marijuana (up to 20%+ THC)



marijuana concentrate (40-80%)
"budder," "butane honey oil"

hashish (~2-20%)
hash oil, marijuana concentrate (40-80%)



cannabidiol oil

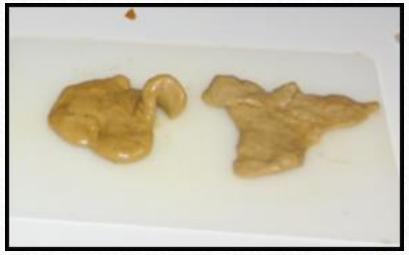
Photo Source: www.dea.gov and cureepilepsy.org

Route of Administration

- Inhalation (smoking, vaporizing)
  - onset: immediate
  - bioavailability: 20-37%

Source:http://www.drugabuse.gov/publications/drugfacts/marijuana

Source: www.dea.gov

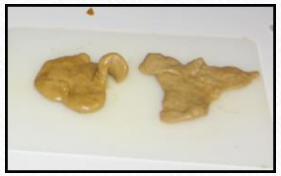


Source:http://www.doh.wa.gov/YouandYourFamily/Tobacco/OtherTobaccoProducts/ECigarettes

Source:http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm172906.htm

Route of Administration

- Oral
  - Onset: 30-60 minutes
  - Bioavailability: 10-20%
- Oro-mucosal: similar to oral; highly variable



Source: www.containerstore.com

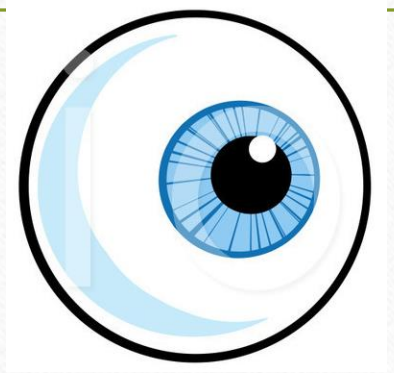
Source: www.dea.gov

Route of Administration

- Topical
  - Onset: ? ~1-2h
  - Bioavailability: ?
    - Bypasses first pass
    - Crossing aqueous layer is the rate limiting step, then perfuses well

Source: www.containerstore.com

Source: http://www.jupitercompounding.com/



Eyeballing* the Math

- 2-3mg → euphoria/cognitive effects
  - impairment = ~~0.05-0.08 BAC*
- "joint" with 500mg of THC
  - Inhalation: 100-185mg if consume ALL
  - Oral: 50-100mg
- 1 gram of 80%-THC marijuana oil = 800mg
  - Inhalation = 160-296mg
  - Oral: 80-160mg

**gross oversimplification, ignoring other modifying factors (other cannabinoids present, genetic variables, drug interactions, chronicity of use, etc.)*

Sites of Action

affects nearly every major organ system

CB1:

Brain
Kidneys
Liver
Heart
GI Tract
Pancreas
Adipose
Muscle
Reproductive organs
Other?

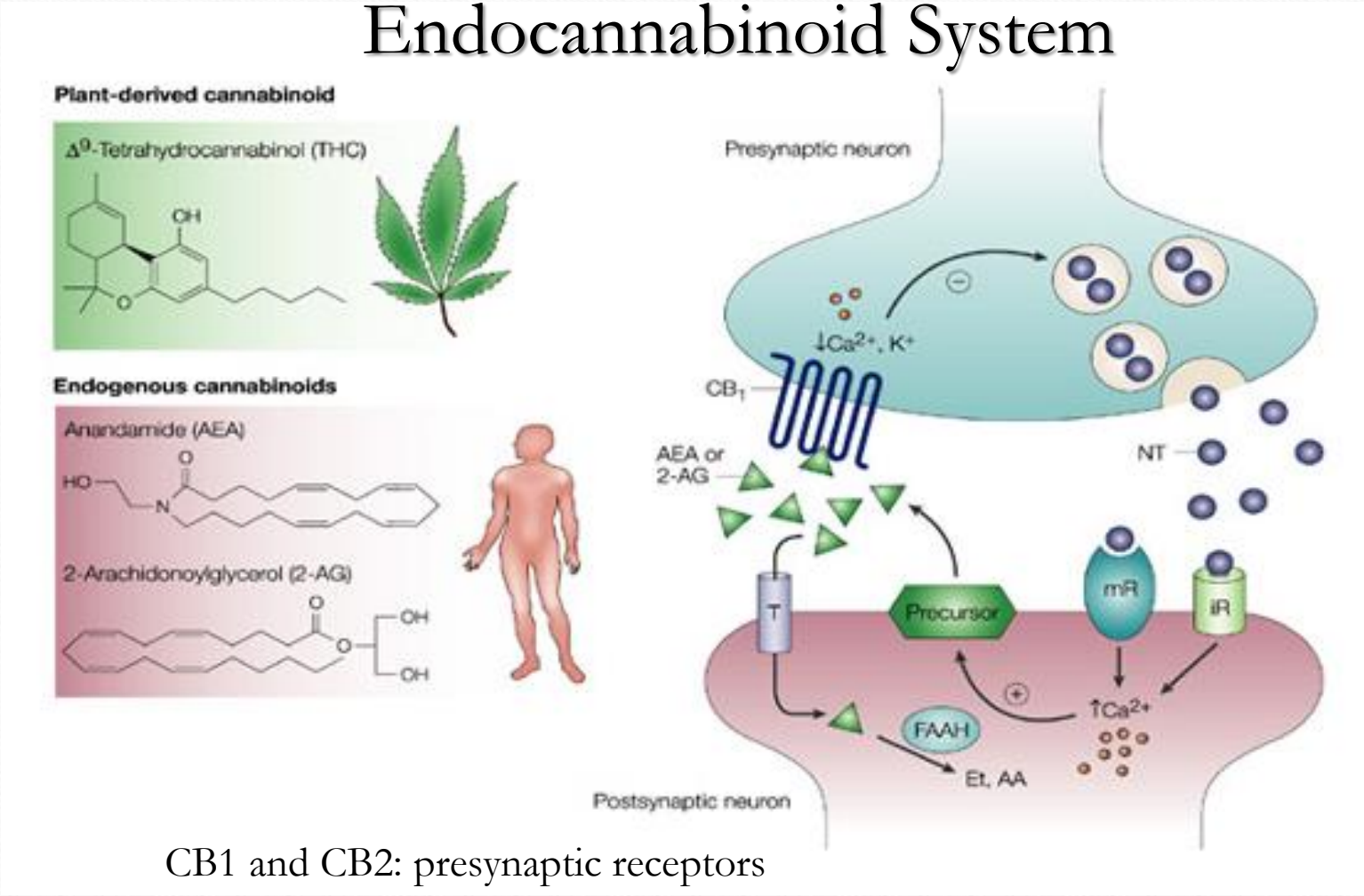
CB2:

Immune cells (T cells, B cells, monocytes)
Spleen
Tonsils
Brain
Heart
Liver
Lungs
Other?

As-of yet unidentified receptors?

Activity on non-cannabinoid receptors?

Endocannabinoid System



?

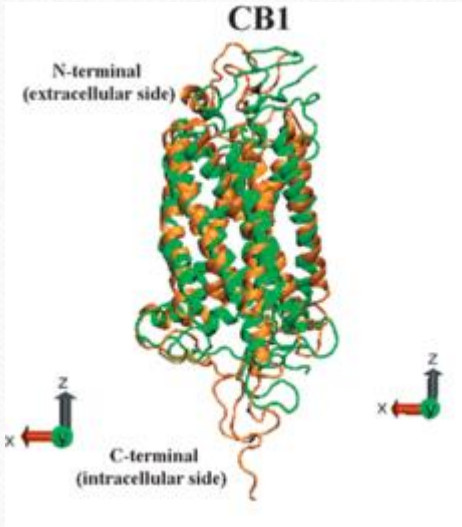
CB1 and CB2: presynaptic receptors
Depending on site, inhibit neurotransmitter release
(GABA, glutamate, 5HT, DA, ACh)

Picture: Nature Reviews Cancer 3, 745-755 (October 2003)

Signaling & Mechanism

CB 1 Receptor

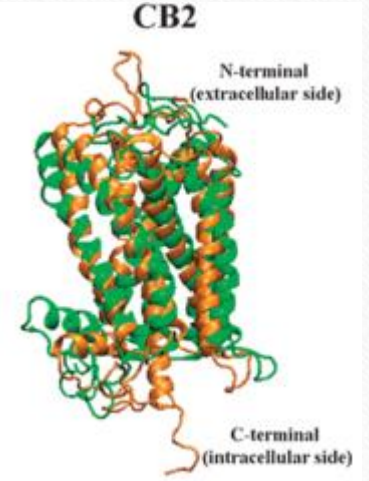
- Expressed presynaptically at glutaminergic and GABAergic interneurons
  - acts as neuromodulator to inhibit release of glutamate and GABA
- Direct stimulation of glycine receptors modulating NMDA receptor responses
- Reduce stress response by inhibiting noradrenaline release from presynaptic terminals



Signaling & Mechanism

CB 2 Receptor

- Increase release of endogenous opioids from keratinocytes and immune cells, which in turn reduces nociceptor activation
- CB2 also located in neuronal circuits in brain relevant for pain control, reward centers.



Qualifying Conditions

1. AIDS
2. Alzheimer's disease
3. Amyotrophic lateral sclerosis
4. Cancer
5. Chronic traumatic encephalopathy
6. Crohn's disease
7. Epilepsy or another seizure disorder
8. Fibromyalgia
9. Glaucoma
10. Hepatitis C
11. Inflammatory bowel disease
12. Multiple sclerosis
13. **Pain (chronic & severe or intractable)**
14. Parkinson's disease
15. Positive status for HIV
16. Post-traumatic stress disorder (PTSD)
17. Sickle cell anemia
18. Spinal cord disease or injury
19. Tourette's syndrome
20. Traumatic brain injury (TBI)
21. Ulcerative colitis

Why do People Use Medical Marijuana?

REASON FOR USE	% REPORTING REASON
Pain Relief	82.6%
To Sleep	70.6%
To Relax	55.6%
Muscle Spasms	41.3%
Anxiety	38.1%
To Stimulate Appetite	38.0%
Nausea	27.7%
Depression	26.1%

SOURCE: Reinarman et al., 2011 (reference list).

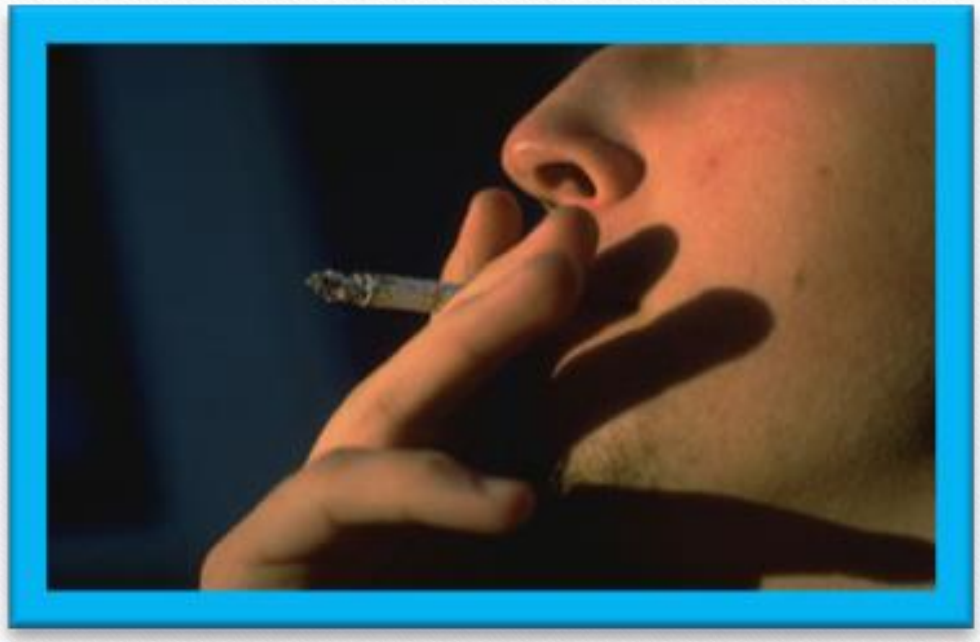
Why do People Use Medical Marijuana?

DISORDER THAT REQUIRES TREATMENT	% CITING AS REASON FOR MJ USE
Chronic Pain	58.2%
Mental Health Disorders	22.9%
Sleep Disorders	21.3%
Neurological Disorders	16.6%
HIV	1.6%
Cancer	1.5%
Glaucoma	1.3%

SOURCE: Reinarman et al., 2011 (reference list).

How do People Use Medical Marijuana?

- 67% of medical marijuana patients use the drug daily
- Over 86% smoke the drug



SOURCE: Reinarman et al., 2011 (reference list).

Preclinical Evidence

- Cannabinoids showed efficacy in rodent acute pain models (formalin test, hot plate, tail flick), chronic inflammatory and neuropathic pain

- Genetic models - deletion of CB1, CB2 causes nociceptor hypersensitivity

Evidence in Humans

- Functional MRI studies show reduced connectivity in pain matrix of brain
- 6 controlled studies in healthy humans in past 10 years
- Lack of robust analgesic effects
  - Effects include:
    - hyperalgesia
    - lack of analgesia
    - moderate analgesia
  - Nearly always associated with analgesia in open-label or retrospective reports

Studies of Effects on Pain

- Lit review of cannabinoids given by any route for treatment of pain Campbell et al. BMJ 2001;323:1-6
- 9 RCTs, 222 patients, 5 trials cancer pain; 2 chronic non-malignant pain; 2 post-operative pain; none evaluated cannabis
- "Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the CNS that limit their use. In acute postoperative pain they should not be used. Before cannabinoids can be considered for treating spasticity and neuropathic pain, further valid randomized controlled studies are needed."

Summary of Randomized Controlled Trials for Pain

Whiting PF et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA*. 2015; 313(24):2456-2473.

Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. *JAMA*. 2015;313(24):2474-2483.

- cannabis: 0 RCT for chronic pain, 3 for neuropathic pain
- nabilone/dronabinol/nabiximols: 6 RCT for chronic pain, 2 for neuropathic pain
- n = 13-63
- duration: 2-15 weeks
- "low" to "moderate" quality data

Since then…

Ware MA, et al. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). *The Journal of Pain*. 2015;15(12):1233-1242.

- Prospective cohort study, chronic non-cancer pain
  - Primary endpoint: adverse effects
  - Secondary endpoints: neurocognition, pulmonary function, efficacy, labs

- Limitations:
  - Powered for n = 350. Starting n = 215. Finishing n = 138.
  - Study and control groups not matched for age, gender, disability, tobacco, alcohol, opioids, antidepressants, anticonvulsants, etc.
  - High drop out rate (30%)
  - Dose ranged 0.1-13.4 grams/day despite regulated product (11-14% THC)
  - Inconsistent mechanism of consumption
  - Didn't administer all screening to all patients

Absence of Quality Evidence

- Few randomized controlled trials
- Poor study design
- Small n
- Short duration
- Difficult to blind
- Wide range of products, doses, routes of administration
- Poor tolerability, high drop out rates

EJP
European Journal of Pain

REVIEW ARTICLE

Current evidence of cannabinoid-based analgesia obtained in preclinical and human experimental settings

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2 Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Project Group Translational Medicine and Pharmacology TMP, Frankfurt am Main, Germany

Table 1 Human experimental studies of the analgesic effects of cannabinoid-based drugs reported during the last 10 years.

Substance	Dose	No. Subjects (men)	Pain model	Analgesic effect	Reference
Cannabis (smoked)	0, 2, 4, 8%	15 (11)	Intradermal capsaicin, heat, electrical and mechanical stimuli	Modest analgesia with the medium dose, hyperalgesic effects of the high dose	Wallace et al. (2007)
Cannabis extract calibrated on THC (oral)	20 mg	18 (0)	UV-B, heat, electrical and mechanical pain stimuli	No analgesic effect in all models; hyperalgesic effects in the electrical pain model	Kraft et al. (2008)
Nabilone (oral)	0.5, 1 mg	17 (7)	Tonic heat pain and contralateral cold water immersion	No analgesic effects and no interaction with descending noxious inhibitory control	
Dronabinol (oral)	15 mg	12 (12)	Topical capsaicin punctate pressure	Reduction in the unpleasantness but not of the intensity of mechanical stimuli, inhibitory effect on pain matrix brain connectivity	Lee et al. (2013)
Dronabinol (oral)	20 mg	30 (15)[a]	Electrical stimuli	Hyperalgesic effects	Walter et al. (2016, 2015)
		15 (8)[a]	Intranasal gaseous CO_2-stimuli	No significant analgesia, inhibitory effect on pain matrix brain connectivity	
Cannabis (smoked)	0, 3.5, 5.6%	42 (21)	Cold-pressor test	Analgesic effects only in men	

Evidence in Humans

- 28 RCT's with 2454 patients with chronic pain
- Cannabinoids associated with greater reduction in pain (37% vs. 31%, OR 1.41) and greater average reduction in numerical pain ratings (−0.46) versus placebo.

Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

Cannabis and Opioids

- Decreased need for opioids after starting medical cannabis
- Significantly reduced prescription pain medications at state level
- Lower annual opioid overdose mortality rates
- Lower percentage of drivers testing positive for opioids after traffic fatalities

Cannabinoid-Opioid Synergy

- Opioid and cannabinoid receptors are both present in pain signaling regions of the brain and spinal cord.
- Opioid and cannabinoid signaling pathways interact with each other.
- Administering cannabinoids with opioids results in a greater than additive antinociceptive (anti-pain) effect.

Cichewicz, 2004

Endocannabinoid Neurophysiology Summary

- Retrograde synaptic transmission
- Neuroprotection
- Neuroplasticity
- Autonomic regulation
- Antinociception
- Synergy with opioid system

Smoked Cannabis for Chronic Pain Safety Study

- 215 chronic pain patients in cannabis group, 216 controls (non-cannabis) studied for 1 year
- No difference in risk of serious adverse events
- Medical cannabis users were at increased risk of non-serious AEs – adjusted IRR=1.73, 95% CI=1.41-2.13 – most were mild to moderate – Headache, nasopharyngitis, nausea, somnolence, and dizziness were the most common AEs reported

Ware et al., 2015

Smoked Cannabis for Chronic Pain Safety Study

- Cannabis group: significant improvements in – pain intensity – physical dimension of quality of life – sensory component of pain – symptom distress – total mood disturbance
- Neurocognitive function improved in both groups.
- No impact of medical cannabis use on measures of hematological, biochemical, liver, renal and endocrine function.

Ware et al., 2015

Marijuana: Immediate Effects

Altered Mood	Reduced Anxiety
Cognitive Impairment (Attention, Judgment)	Sedation/Drowsiness
Altered Perception	Sensory Intensification
Impaired coordination/balance	Increased heart rate
Hunger	Hallucinations (in large doses)

- Effects can vary by strains
  - *Sativa*: More euphoria, stress relief
  - *Indica*: Relaxation, physical (especially pain) relief
  - *Sativa* and *Indica* often combined, leading to variable effects

SOURCES: NIDA 2012a;b (reference list).

Adverse Effects: Short-term

- anxiety, panic attacks
- distorted perception, hallucinations
- increased heart rate and blood pressure
- decreased memory & learning
- difficulty thinking & problem solving
- decreased coordination
- visuomotor skills deficit

Effects transient, resolve without intervention.

Actual impairment persists past perceived impairment

Effects primarily associated with THC

Adverse Effects: Long-term

"associated with"

- immunosuppression
- inhalation: increased risk cancer of head, neck, lungs, respiratory tract
- increased risk testicular cancer
- occlusion brain arteries, increased stroke
- oculomotor control deficit
- hyperemesis syndrome

Adverse Effects: Long-term, continued

"associated with"

- Neurological changes
  - **sustained decreased IQ**[17]
  - adolescents: change in neuroanatomy?
  - **altered memory, primarily verbal**[19]
  - decreased cerebral blood flow
  - decreased neural efficiency
  - **increased DA neurotransmission, psychosis, anxiety disorder(s), schizophrenia**

younger age + extent of use —genetics→ mental illness

Marijuana: Negative Effects on Behavior and Mental Health

- Similar to alcohol/other drugs if misused (impairment)
- Long term use has negative impact on learning and memory
- Long term use reduces motivation ("amotivational syndrome")
- Associated with mental health problems
  - Unclear if marijuana use is cause or effect
  - Heavy use is highly associated with serious mental illness – particularly among those with high risk (e.g., family history)

SOURCES: Ben Amar, 2006; Bostwick, 2012; NIDA, 2012a, 2012b (reference list).

Marijuana: Negative Effects When Smoked

- Can lead to respiratory illness
  - One marijuana cigarette causes as many pulmonary problems as 4-10 tobacco cigarettes
  - Increased risk for bronchitis, emphysema, lung cancer
- Can cause cardiovascular complications
  - Raises blood pressure & heart rate 20-100%
  - 4.8 times risk of heart attack in hour after use

SOURCES: Ben Amar, 2006; Bostwick, 2012; NIDA, 2012a, 2012b (reference list).

Marijuana:
Negative Effects in Pregnancy

- There is increasing evidence that prenatal exposure may result in:
  - Increased risk of motor, social, and cognitive disturbances.
  - Higher rate of low birth weight infants, and childhood leukemia
- Marijuana has been found in breast milk although levels are generally considered subclinical.

SOURCE: Texas Tech University, Health Sciences Center, 2013 (reference list).

Drug-Cannabis Interactions:

"Pain" Medications

Medication	Nature of Interaction	Potential Outcome
Acetaminophen	CNS depression CYP2E1	sedation, impaired, etc ↓APAP efficacy
NSAIDs	CNS depression combined renal assault	impaired, falls renal impairment, etc.
Anticonvulsants	CNS depression carbamazepine/CYP3A4	impaired, falls ↑cannabis metabolism
TCAs	CNS depression Anticholinergic	impaired, falls ↑hr, arrhythmia, slow GI, delirium
Other antidepressants	CNS depression duloxetine/CYP1A2	impaired, falls ↓duloxetine effect
Opioids	CNS depression	impaired, falls, respiratory depression, death (?)

Monitoring Recommendations

- Monitor if concurrent medication/condition where therapeutically important
- Recheck cannabinoids in urine drug screen (UDS)
  - 1 month if sparing use
  - 2 months for chronic use
- Know your UDS: screen vs confirmation?
  - If have THC quantification test
    - Trend more important than actual number
    - Change by 50% represents change in pattern of use

Marijuana: Potential for Abuse/Dependence

- Regular and prolonged use can change the way the brain works, leading to abuse or dependence
- Marijuana abuse/dependence most common among individuals with mental health disorders
- In 2011, 22.9% of people in US who received addiction treatment received treatment for marijuana use disorders
- Average adult entering treatment for marijuana abuse/dependence has used daily for ten years, tried to quit six times

SOURCE: Compton et al., 2004; NIDA, 2012a, 2012b; SAMHSA, 2012 (reference list).

Marijuana Abuse/Dependence

DRUG	LIFETIME RISK OF DEPENDENCE
Nicotine	32%
Heroin	23%
Cocaine	17%
Alcohol	15%
Marijuana	9%

SOURCE: Bostwick, 2012 (reference list).

Marijuana: Signs of Abuse/Dependence

- Tolerance/withdrawal
  - Anger or Aggression
  - Decreased Appetite / Weight Loss
  - Irritability
  - Nervousness / Anxiety
  - Restlessness
  - Sleep Difficulties / Strange Dreams
- Preoccupation
- Loss of control
- Continued use in the face of adverse consequences
- Cognitive distortions/denial

SOURCE: Budney et al., 2004 (reference list).

Marijuana Abuse/Dependence Treatment

- Treatments are behavioral
  - Motivational Enhancement Therapy
  - Cognitive Behavioral Therapy
  - Contingency Management
  - Family-based Treatment
- Only 10-30% success rate in achieving abstinence from marijuana after one year
- No medications available, but drugs to treat withdrawal symptoms in development

SOURCE: NIDA, 2012b (reference list).

Addiction Treatment Options

- No medication-assisted treatment needed (nor effective) for cannabis addiction

- Addiction Treatment:
  - Cognitive Behavioral Therapy (CBT)
  - recovery groups (Marijuana Anonymous)

legal ≠ safe

legal ≠ effective

wide therapeutic index ≠ benign

Pros and Cons of Marijuana

- Not associated with death
- Not as addicting as other drugs
- *Modest* benefit demonstrated for *small* segment of the population in short term use

- Marked negative cognitive effects
- Very dangerous to adolescent brain development and occurrence of mental illness
- Cancer risk
- Driving impairment

To integrate or not, that is the question

- FOR
- Pain is the #1 reason for use of MMJ
- Many of the other approved diagnoses are associated with pain
- Potential tool to add into the pain management armamentarium
- Potential to reduce the opioid burden
- Research opportunity

- AGAINST
- Increased scrutiny from the regulatory board(s)
- No substantial body of evidence
- Long term consequences, complications are unknown

Take-Away Points

- Marijuana is a potentially dangerous drug, with potentially serious physical and mental health consequences
- Unlike other medicines, marijuana has not undergone FDA testing for safety and efficacy
- Since not formally regulated by the FDA, there is no way to know what is actually in the marijuana
- Though legal under several states' laws, medical marijuana is illegal under federal law

Take-Away Points

- Providers should educate patients about the risks associated with medical marijuana, and alternatives to its use
- Providers need to be aware of the signs of abuse/dependence, and know what to do if they identify it
- Providers should weigh pros and cons of marijuana use with their patients, and educate them about potential risks of use
- If the costs of marijuana use outweigh the benefits, providers should work with patients on additional strategies to manage symptoms and discomfort

Research Issues

- MJ is a Schedule I drug – a barrier to conducting prospective RCTs
- Studies are short - two weeks average, ranging from a few hours to one year
- Most studies conducted with oral THC preps rather than smoked cannabis
- Most studies exclude anyone with a history of major psychiatric disorder other than depression and/or history of substance abuse
- Most studies done to date:
  - Short in length (average two weeks)
  - Small N (lacking power)
  - Retrospective in nature
  - Confounded by uncontrolled variables
    - Concomitant tobacco use
    - Comorbid illnesses

Current Medical Marijuana Laws

- 21 States and D.C. for medical marijuana and another 10 for rec/med
- They vary in degree and implementation
  - Started as “affirmative defense” for marijuana use for medicinal purposes; or removal of criminal penalties if “medical” use is claimed
  - Evolved into state-based production and distribution
- Rely not on the FDA, but unregulated businesses

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Other Resources

- US National Library of Medicine, National Institutes of Health
- Drug Enforcement Administration (DEA)
- Substance Abuse and Mental Health Services Administration (SAMHSA)
- National Institute on Drug Abuse (NIDA)
- National Alliance on Mental Illness (NAMI)