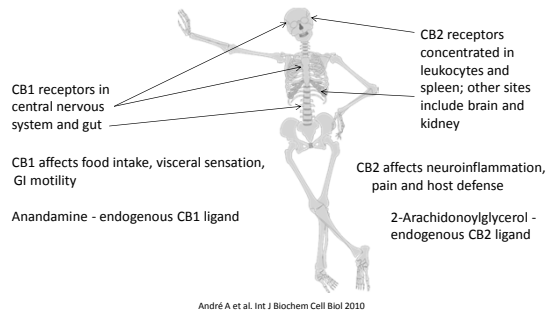


Endocannabinoid System



Cannabinoids in Marijuana

- Marijuana contains more than 80 different cannabinoids
- THC and cannabidiol are the most common cannabinoids
- Also contains terpenes and aldehydes

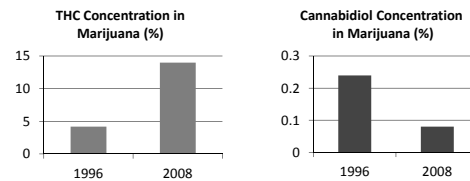
1. Maa E, et al. Epilepsia
2. Niesink RM, et al Frontiers in Psychiatry 2013

THC vs. Cannabidiol

- THC (Delta-9 tetrahydrocannabinol)
 - Responsible for the "high" of marijuana
 - Short term effects include:
 - Euphoria
 - Altered senses and altered sense of time
 - Impaired body movement
 - Memory impairment
- Cannabidiol
 - Regulates response to THC
 - Decreases psychoactivity
 - Reduces craving and risk of addiction

Hall W, et al. Lancet. 2009

Changes in THC and Cannabidiol



Burgdorf JR et al. Drug Alcohol and Dependence 2011

Cannabis Types

Sativa	Indica
Taller plant with longer narrower leaves	Shorter, bushier with short wide leaves
More euphoria	More relaxation
More effects on brain function	More body effects
Increased energy	More somnolence
May cause spacey feeling	Appetite stimulant
Commonly used for daytime	Commonly used at night

Erkelens JL. Cannabinoids 2014

Cannabinoid Formulations

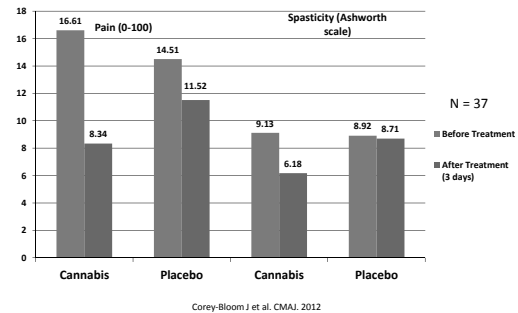
Cannabinoid	Dosage and Components	Use In Selected Trials	Cost
Marijuana (Cannabis)	THC content varies THC/cannabidiol varies > 80 cannabinoids May be smoked, vaporized or oral	1%-8% THC 1-3 cigarettes/day	\$8-25 /day
Nabiximols	Δ^9 -THC 2.7 mg/ CBD 2.5 mg/spray	Max 65 mg/d Max 120 mg/d	\$40/day
Dronabinol	2.5 mg Δ^9 -THC	Max 10 mg/d Max 20 mg/d	\$1.8/mg \$5-36/day
Nabilone	1 mg synthetic cannabinoid	1 mg bid 0.5-1 mg hs	\$10-40/day

Price data for marinol and marijuana from ProCon.org

Medical Uses of Cannabinoids

- Good Evidence: MS, Neuropathic pain
- Fair Evidence: Crohns disease, CINV, Pediatric epilepsies
- Weak Evidence: Fibromyalgia, Cancer pain, Huntingdon chorea
- Anecdotal reports: TNTC (Adult epilepsy, Tourette Syndrome, PTSD, Parkinson disease, ALS, Anxiety, Back pain and many others)

Smoked Marijuana for MS



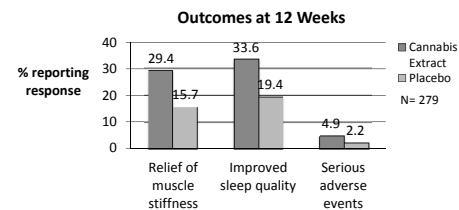
Nabiximols vs. Placebo for MS

- 187 MS patients with painful spasms randomized to oromucosal spray (nabiximols) vs. placebo (2:1) for 6 weeks
- Dose titrated to maximum 48 sprays/day
- Better outcomes on Numerical Rating Scale with spray
- Open label extension for ~ 1 year
 - No significant adverse events
 - No evidence of tolerance developing
 - Average dose 7.3 sprays/day

Collin C et al. European Journal of Neurology 2007

MUSEC

- RCT of stable MS patients given oral cannabis extract (THC 2.5 mg plus cannabidiol 0.8-1.8 mg)
- Improved muscle stiffness and sleep ($p < 0.025$)
- No difference in adverse events



Recommendations

- Nabiximols (oral mucosal spray) may be offered to reduce symptoms of spasticity, pain, or urinary frequency (AAN Level B)
- Smoked cannabis has inadequate data for spasticity, pain, balance/posture, and cognition (AAN Level U)
- EFNS recommends cannabinoids in MS (level A) only if all other treatments fail

Yadav V et al. Neurology 2014
Attal et al. Eur J Neurol 2010

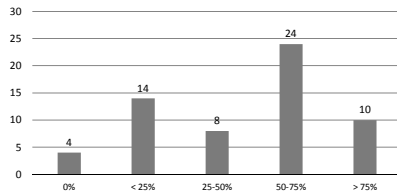
Treatment Resistant Pediatric Epilepsy

- 137 patients (mean age 11) given cannabidiol 2-5 mg/kg/day for 12 weeks as add-on therapy
- 20% with Dravet syndrome, 19% with LGS
- Median monthly motor seizures decreased from 30 to 15.8
- Median 36.5% decrease in monthly motor seizures
- Weeks 8-12
 - 11% were free from motor seizures
 - 7% were free from all seizures

Devinsky O, et al. Lancet Neurol 2015

CBD/THC 20:1 Cannabis Oil

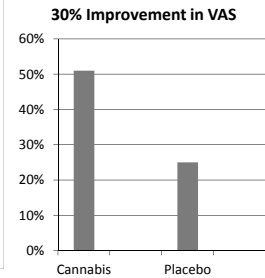
Seizure reduction in 74 patients
refractory to ≥ 7 antiepileptic
drugs



Tzodok M, et al. Seizure 2016

HIV-associated Pain

- Systematic review
- 2 placebo-controlled RCTs with 122 patients of smoked cannabis
- NNT 3 (95% CI 2.2-7.5)



Phillips TJ et al. PLoS One. 2010;

HIV-associated Polyneuropathy

- EFNS found efficacy only for
 - Lamotrigine (in patients on ART) (Level B)
 - Smoking cannabis (Level A)
 - Capsaicin patches (Level A)

Attal N et al. Eur J Neurol 2010 Sep;17(9):1113

Oncology Symptoms

- Israeli survey data of 17,000 cancer patients at single institution
 - 279 (< 1.7%) received a permit for cannabis from an oncologist
 - Median age 60 years
 - 84% had metastatic disease
 - Improvement in pain, general well-being, appetite and nausea were reported by 70%, 70%, 60% and 50%, respectively

Waissengrin B et al. J Pain Symptom Manage. 2014

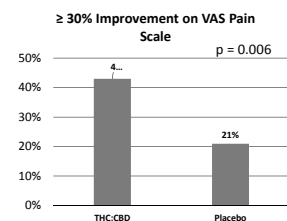
Cancer Chemotherapy-Induced Nausea and Vomiting (CINV)

- 2 crossover trials of smoked THC vs. placebo
 - 6% vs. 72% in 15 patients with osteogenic sarcoma treated with MTX¹
 - No benefit in 8 patients with soft tissue sarcoma treated with AC²
- Oromucosal spray as add-on therapy to 5-HT₃ receptor antagonists or NK1 inhibitors in trial of 16 patients with solid tumors³
 - Complete response in 71% vs. 22%
 - 1/7 withdrew due to adverse events

1. Chang AE et al. Annals of Internal Medicine 1979
2. Chang AE et al. Cancer 1981
3. Duran M, et al. British Journal of Clinical Pharmacology. 2010

Cancer Pain

- No RCTs using smoked cannabis
- RCT of 177 patients
 - oromucosal spray
 - THC
 - Placebo



Johnson JR et al. J Pain Symptom Manage 2010

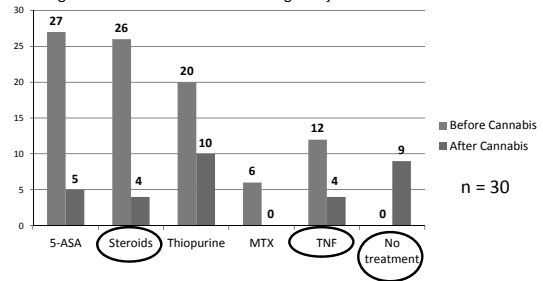
Cancer Use Recommendations

- American Society of Clinical Oncology (ASCO)¹
 - Reserve cannabinoids for patients intolerant or refractory to 5HT3 receptor antagonists, NK-1 receptor antagonists, and dexamethasone
- National Comprehensive Cancer Network (NCCN)²
 - Synthetic cannabinoids (dronabinol and nabilone) useful as treatment options for breakthrough nausea and vomiting
 - Not recommended as part of guidelines for management of antiemesis
- Multinational Association of Supportive Care in Cancer (MASCC) and ESMO³
 - Consider cannabinoids a possible option for refractory nausea and vomiting and as rescue antiemetic

1. Kris MG et al. J Clin Oncol 2006
2. Todorov B. J Natl Compr Canc Netw 2012
3. Rolla F et al. Ann Oncol 2010

Intractable Crohn's Disease

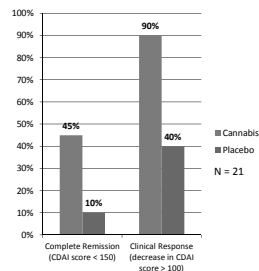
Change in Medication Use After Starting Marijuana



Naftali T et al. Isr Med Assoc J. 2011

Cannabis For Intractable Crohn's Disease

- 21 patients with refractory disease
- Cannabis smoking BID vs. placebo
- 8 week study
- Crohn's Disease Activity Index used as outcome
- Differences not significant



Naftali T et al. Clin Gastroenterol Hepatol. 2013

Most Common Medical Diagnoses For California Medical Card

- Chronic pain conditions (58%)
- Mental health disorders (23%)
- Insomnias (21%)
- GI disorders (13%)
- Neurologic disorders (17%)
- Gynecological disorders (8% of females)

Nunberg et al. J Drug Policy Anal 2013

Recreational Marijuana

- Legalized before 2016 in AK, WA, OR, CO, DC DC
- Ballot measures Nov 2016 in CA, AZ, ME, MA, and NV
- Effects of legalization on use uncertain
 - Increases in use may reflect substitution for EtOH
 - Some increase in adverse events noted
 - Increases in accidental ingestions
 - Increase fatal crashes with drivers positive for marijuana

Adverse Effects of Cannabis

- Short-term effects
 - Dizziness
 - Impaired motor coordination
 - Altered judgment
 - Euphoria, disorientation
 - Increased appetite
 - ↑ HR & BP; Vasodilation
 - Psychosis
 - MVA
- Long-term effects
 - Psychosis
 - Pulmonary effects
 - Hyperemesis

1. Volkow ND et al. NEJM 2014
2. Wilcock A et al. Journal of Pain and Symptom Management 2013

Psychosis

- Risk of acute cannabis psychosis while intoxicated that can last 24-48 hours
 - Persistent psychotic symptoms lasting beyond the period of acute intoxication
 - Paranoia, disorganized thinking, persecutory and grandiose delusions, hallucinations, and cognitive impairment
- Risk of psychosis related to THC concentration and THC/CBD ratio
- Increased risk for schizophrenia in at-risk users

Bui QM, et al. Western Journal of Emergency Medicine 2015

Pulmonary Effects

- Chronic bronchitis symptoms may develop
- Chronic use
 - No increase in airway obstruction or COPD
 - No clear association with lung or upper airway cancer
 - May increase risk for URI and pneumonia
 - Overall significantly lower risks than tobacco
- Symptoms usually resolve with abstinence

Tashkin DP. Ann Am Thorac Soc 2013;10:239-247

Cannabinoid Hyperemesis Syndrome

- Cyclic vomiting
- Abdominal pain
- Compulsive showering
- Improvement of symptoms with cessation of cannabis
- Rates doubled in CO following legalization

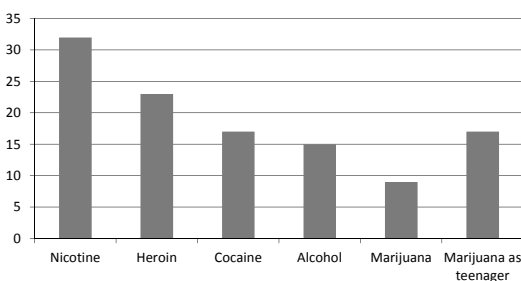
Kim HS et al. Acad Emerg Med. 2015 Jun;22(6):694-9

Addiction

- Marijuana use can result in:
 - Craving
 - Tolerance
 - Dependence
 - Continued use despite adverse effects on one's life
- Withdrawal symptoms
 - Irritability
 - Sleeping difficulties
 - Dysphoria/anxiety

Volkow ND, et al. NEJM 2014

Lifetime Dependence Risk (%)



Bostwick JM. Mayo Clin Proc. 2012

Driving Issues

- Risk of MVA
 - increased 2-2.6X
 - MJ < EtOH < EtOH + MJ
- Legal limit = 5 ng/mL of THC in CO & WA
- THC 3.5 ng/mL = BAC 50
- Duration of impairment
 - Smoking: 4 hours
 - Edibles: 12 hours

1. Li M et al. Epidemiol Rev 2012
 2. Wolff K et al. Drug Testing and Analysis 2013
 3. Romano E et al. J. Stud. Alcohol Drugs 2014

Accidental Ingestion

- Biggest concern is edibles
- Unintentional MJ exposure in children < 6 more than doubled from 2006-2013
- Poison Control Center calls for MJ exposure 1 year after legalization
 - 71% increase in CO
 - 55% increase in WA

Orders B et al. Clin Pediatr 2015

Smoking marijuana

- Most common method of consumption
- No filters
- Inhale deeply and hold
- Pharmacokinetics
 - Peak plasma in 10 min
 - 1-4 ng/mL at 3-4 hours
- Associated with lung irritation from by-products

Vaporization

- Marijuana leaves and buds heated but not burned
- Volatile chemicals, including THC and CBD are released
- Vapor is inhaled
- Approach is similar to smoking but considered less irritating to lungs (lower CO levels)

Edibles

- Raw marijuana not used
- Marijuana heated in butter or oil
- Butter or oil is then used in preparing edibles
- Pharmacokinetics
 - Onset of action 30-90 minutes
 - Peak effect 2-3 hours
 - Duration 4-12 hours

Different kinds of edibles

- Commercial edibles
 - Baked goods, such as cookies or brownies
 - Candies: caramels, gummies, hard candies or lollipops
 - Chocolates: bars, truffles
 - Energy bars
 - Cooking ingredients such as honey, ghee, olive oil
- Marijuana Tea
 - May be steeped in hot water to make tea
 - Addition of alcohol or oil needed to extract cannabinoids

Problems with edibles

- Problems with delay in effect
 - Titration difficult
 - May lead to excessive use to try to achieve effect
- Dosing
- Accidental ingestion
- Accuracy of dosing information reported to be poor
 - 17% accurately labeled
 - 23% under labeled
 - 60% over labeled

Vandrey R. et al. Jama 2015

Summary

- Marijuana has been tried for many medical conditions but high-quality evidence is limited
- Recreational marijuana and Medical marijuana have same modes of ingestion and same adverse effects
- Legalized marijuana associated with increased accidental ingestions. Awareness of risks is key.