Getting High or Getting Better: The Dope on Medical Marijuana

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Consulting:
DepoMed
Lilly

Stock:
Pfizer (small)

Disclosures
Overview

- Historical overview of cannabis (marijuana)
- Early use of cannabis in western medicine
- Forms of marijuana
- Proposed benefits & harms
- Clinical trial data & medical marijuana
- Comments on evolution of cannabinoids
# Federal Controlled Substance Schedules

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Accepted medical use?</th>
<th>Potential for Abuse, addiction or physical dependence</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule 1</td>
<td>No</td>
<td>High</td>
<td>Marijuana, LSD, Heroin, Mescaline</td>
</tr>
<tr>
<td>Schedule 2</td>
<td>Yes</td>
<td>High</td>
<td>Morphine, oxycodone, methadone, cocaine, hydrocodone/acetaminophen</td>
</tr>
<tr>
<td>Schedule 3</td>
<td>Yes</td>
<td>Less than schedule 1 &amp; 2</td>
<td>Opioids combined with a non-opioid; Codeine combinations</td>
</tr>
<tr>
<td>Schedule 4</td>
<td>Yes</td>
<td>Less than schedules 1-3</td>
<td>Benzodiazepines, chloral hydrate</td>
</tr>
<tr>
<td>Schedule 5</td>
<td>Yes</td>
<td>Less than schedules 1-4</td>
<td>Antitussives with limited amounts of codeine</td>
</tr>
</tbody>
</table>
Comparative Danger and Dependence

Overall Drug Harm Score

Presidential Support for ‘Hemp’

“Some of my finest hours have been spent on my back veranda, smoking hemp and observing as far as my eye can see”

Thomas Jefferson, 1781

The authenticity of the quote is questioned but there is no doubt he did grow hemp.
Presidential Support for ‘Hemp’
Or Not.....
Presidential Support for ‘Hemp’
Or yes
Presidential Support for ‘Hemp’

Barack Obama reading from his book ‘Dreams from My Father’
Early Historical Use of Cannabis

Cannabis is an ancient drug and was probably the first crop to be grown for reasons other than food production.

Cannabis is found in ancient Arabic, Persian and Hindu scriptures.

Galen and Hippocrates prescribed cannabis.

Philip Robson, Forbidden Drugs, Oxford University Press, Oxford 1999, p66

Mr Hem Chunder Kerr, Deputy Collector on Special Duty, 2 April 1877, in 'Papers Relating to the Consumption of Ganja and Other Drugs in India', British Parliamentary Papers, LXVI, p100
Early Historical Use of Cannabis

The first medicinal use is recorded in a Chinese document from the first 2 centuries AD, states passed down from Emperor Shen Nuang in the 3rd millenium BC.

Emperor Shen Nuang (2838-2698 B.C.)

Li, HL. An archaeological and historical account of cannabis in China. Econ. Bot. 1974;28:437-448
Hildegard was the first major German mystic; a proliferative writer, philosopher, prophet, poet, dramatist and physician. From age 6 began having visions, which she said came straight from God. Her visions were pivotal in directing her to a life of mysticism.

From Physica—“Whoever has an empty brain and head pains may eat it [cannabis] and the head pains will be reduced”
Introducing Cannabis into Western Medicine

Dr. O'Shaughnessy’s 1839 paper caused a sensation when it became widely available in England. Physicians throughout Europe and America tried cannabis for a huge variety of illnesses.

Also introduced electrolyte replacement for cholera and the introduction of the telegraph to India for which he was knighted by Queen Victoria

W. B. O'Shaughnessy, MD (1809-1889)

Sir John Russell Reynolds

Attempted to define a legitimate medical use for marijuana

“Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess”

Treated migraine, neuralgia, cramps, dysmenorrhoea

President of the British Medical Association
& College of Physicians (London)

Reynolds JR. On the therapeutic uses and toxic effects of cannabis indica. Lancet 1890;135:637-8
"The headache to which I wish to draw attention is of a dull, continuous or subcontinuous character, attended sometimes with paroxysmal exacerbations".

"..may last weeks, months or even years"

Describes a regimen of increasing doses of cannabis, twice daily.
The drugs of which I wish to speak to-night, and which I have used for several years, are belladonna and cannabis indica. Belladonna has a sedative action on the uterus and pelvic contents, and relaxes rather than constipates the bowels. Its value in irritable conditions of the bladder and urethra is well known. This combination of qualities is called for in a very large number of women. Cannabis indica has somewhat similar properties, and especially for sensitive ovaries and in the various painful affections of those organs its use is often productive of much good. It has few equals in its power over nervous headaches such as women with pelvic trouble are subject to. It has seemed to me that these two drugs were capable of performing excellent service in gynecological practice.

During the paroxysm the patient should be kept in bed and absolutely quiet. If the patient feels faint and nauseated a small cup of hot, strong coffee or 20 drops of chloroform give relief. Cannabis indica is probably the most satisfactory remedy. Seguin recommends a prolonged course of the drug. Antipyrin, antifebrin, and phenacetin have been much used of late. When given early, at the very outset of the paroxysm, they are sometimes effective. Small, repeated doses are more satisfactory. Of other remedies, caffeine, in 5-grain doses of the citrate, nux vomica, and ergot have been recommended. Electricity does not appear to be of much service.
Cannabis for Headache

**HEADACHE AND HEAD PAINS**

A Ready Reference Manual for Physicians

by

WALTON FOREST DUTTON, M.D.

F. A. DAVIS COMPANY, PUBLISHERS

PHILADELPHIA

1939

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*Headache and neuralgias* should be relieved by appropriate means, such as one of the following prescriptions:

- **配方**
  - Ext. cannabis indicae .................. gr.iii 0.18
  - Acidi acetylsalicylici .............. 5iss 6.00
  - Quin. hydrobromidi .................. gr.ss 0.03
  - Mix and make capsules no. xx.
  - One every two or three hours as necessary.

- **配方**
  - Ethylmorphinae hydrochloridi... gr.j 0.060
  - Scopolaminae hydrobromidi ...... gr.1/60 0.001
  - Cannabinae (alkaloid) .......... gr.v 0.30
  - Cerii oxalatis ..................... gr.xx 1.30
  - Pone in capsuleae no. xxx.

**HEADACHE AND HEAD PAINS**

- **配方**
  - Ext. cannabis indicae .......... gr.iii 0.18
  - Larodon ........................... 5iss 6.00
  - Quin. hydrobromidi ............. gr.xx 1.30
  - M. et fiant capsuleae no. xx.
  - One capsule every two hours or p.r.n. for headache. (Use cautiously.)
‘Reefer’ in Southern US Culture

‘Reefer Man’ Cab Calloway Orchestra 1933
Harry J. Anslinger
Director of the Federal Bureau of Narcotics (1930-1962)

“I believe in some cases one cigarette might develop a homocidal mania, probably to kill his brother…”

“Probably some people could smoke five before it would take effect, but all the experts agree that the continued use leads to insanity”

Harry J. Anslinger, testimony to US Congress supporting the Marihuana Tax Act, 1937
“Colored students at the Univ. of Minn, partying with female students (white) smoking [marijuana] and getting sympathy with stories of racial persecution. Result pregnancy”

‘Reefer Madness’ (1937)
Inaccurate Portrait of Marijuana
Medical Marijuana in the United States

1996: California
1999: Maine
2000: Colorado, Hawaii, Nevada
2004: Montana
2006: Rhode Island
2007: New Mexico, Vermont
2008: Michigan
2010: Arizona, New Jersey
2011: Delaware, Washington, D.C.
2012: Connecticut, Massachusetts
2013: New Hampshire, Illinois
2014: Maryland, Minnesota, New York
2015: Georgia
Medical Marijuana – What Disorders?

2013 Canadian study on the use of cannabis for therapeutic purposes

Doctor-Patient Communication and First Amendment Rights

- California—medical marijuana in 1996. After DEA threats, physicians brought suit to prohibit the Government from taking action against them for communicating with patients about the medical use of marijuana.

- Trial court—DEA action only permissible if Feds had substantial evidence that the physician ‘aided and abetted the purchase, cultivation, or possession of marijuana’.

- In 2002—9th Circuit Court of Appeals affirmed the injunction, ruling that First Amendment prohibits the government from punishing physicians “on the basis of the content [potential usefulness of marijuana] of doctor-patient communications.

- Little doubt the US Supreme Court would follow it today

Annas GJ. Medical Marijuana, Physicians, and State Law. NEJM 2014;Sept 11th
Inhalation

Oral Ingestion

Vaporizers

Marijuana oil

Baked Goods

Cooking

Tincture of Marijuana
Inhalation

Marijuana oil

Vaporizers

California dispensaries say butane hash oil, or "wax," now accounts for 40% of sales.
Vaporizing Marijuana

From National Geographic Channel’s Drugs Inc. ‘Marijuana’ (2011)
Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

Marcus A. Bachhuber, MD; Brendan Saloner, PhD; Chinazo O. Cunningham, MD, MS; Colleen L. Barry, PhD, MPP

RESULTS Three states (California, Oregon, and Washington) had medical cannabis laws effective prior to 1999. Ten states (Alaska, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Rhode Island, and Vermont) enacted medical cannabis laws between 1999 and 2010. States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; P = .003) compared with states without medical cannabis laws. Examination of the association between medical cannabis laws and opioid analgesic overdose mortality in each year after implementation of the law showed that such laws were associated with a lower rate of overdose mortality that generally strengthened over time: year 1 (−19.9%; 95% CI, −30.6% to −7.7%; P = .002), year 2 (−25.2%; 95% CI, −40.6% to −5.9%; P = .01), year 3 (−23.6%; 95% CI, −41.1% to −1.0%; P = .04), year 4 (−20.2%; 95% CI, −33.6% to −4.0%; P = .02), year 5 (−33.7%; 95% CI, −50.9% to −10.4%; P = .008), and year 6 (−33.3%; 95% CI, −44.7% to −19.6%; P < .001). In secondary analyses, the findings remained similar.

CONCLUSIONS AND RELEVANCE Medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates. Further investigation is required to determine how medical cannabis laws may interact with policies aimed at preventing opioid analgesic overdose.
Beneficial Effects of Marijuana

NERVOUS SYSTEM
- Symptoms of Multiple Sclerosis
- Pain of peripheral neuropathy
- Migraine
- Seizures
- Anxiety & Depression
- Alzheimer’s disease
- Parkinson’s disease

RHEUMATOLOGY
- Joint pains (arthritis)

GASTROENTEROLOGY
- Antiemetic
- Appetite stimulant
- Treat inflammatory bowel disease

OPHTHALMOLOGY
- Reduces IOP, treating glaucoma

CANCER PAIN
Criticisms of Medical Marijuana

- Abuse potential and gateway drug
- Patients want it recreationally
- No dosing control
- Federally illegal!
- Backdoor legalization
- Lack of scientific evidence supporting benefit
- Increased diversion to minors
- Ill effects:
  - Brain maldevelopment or damage
  - Memory and cognitive impairment
  - Lung damage, cancer?
  - Psychosis/Schizophrenia?
Adverse Effects of Marijuana

CENTRAL NERVOUS SYSTEM
- Memory impairment
- Anxiety, panic, paranoia
- Addiction
- Schizophrenia

PERIPHERAL VASCULAR
- Raynauds
- Thromboangitis obliterans

CEREBROVASCULAR
- TIA/Stroke
- RCVS

CARDIOVASCULAR
- Increased angina frequency
- Myocardial infarction
- Cardiomyopathy
- Arrhythmia

RESPIRATORY
- Resp. symptoms
- Bronchitis
- COPD
- Cancer

GASTROENTEROLOGY
- Cannabis hyperemesis syndrome
Pulmonary Effects of Marijuana Smoking

- Increased risk of chronic bronchitis
- No clear link to COPD
- Smoke contains carcinogens
- No demonstrable risk of cancer from light or moderate use
- Evidence mixed on carcinogenic risk of long-term heavy use
- Far lower risk of pulmonary complications than tobacco

Cardiovascular Effects of Marijuana

Several reports note temporal relation between marijuana use and MI in the hour after dosing—many normal coronary arteries

May also precipitate MI in those with CAD

After MI, mortality rate significantly higher in marijuana users

Enhances sympathetic tone

Marijuana increases heart rate and blood pressure

Associations

- Myocardial infarction
- Sudden cardiac death
- Cardiomyopathy
- Stroke/TIA
- Arteritis

Cerebrovascular Effects?

- In a 2007 study of hospital admissions in Texas, cannabis exposure associated with ischemic stroke 1.76 (95% CI 1.15–2.71) adjusted for alcohol and tobacco

- A 2013 prospective case-control study, odds of cannabis associated with cerebrovascular events 1.59 (95% CI 0.71–3.7) not significant, after adjustment for tobacco and other factors

- 2015 systematic appraisal review of 34 case reports on 64 patients in Stroke

Westover AN et al. Stroke in young adults who abuse amphetamines or cocaine: a population based study of hospitalized patients. Arch Gen Psychiatry 2007;64:495-502
Impediments to Cannabis Research

- National Institute of Drug Abuse (NIDA) the sole source of research grade cannabis for all US trials
- NIDA contracts only with University of Mississippi to grow the cannabis-dependent on their strains
- DEA registration for a schedule 1 substance
- IND application on file with the FDA
- Privately funded marijuana studies must go through Public Health Service review in addition to FDA—an extra step that does not exist for research concerning any other drug. That review is mandated by the Department of Health and Human Services, not DEA. REMOVED JUNE 2015
- In the last year the Federal Government has increased production from 46 pounds to 1400 pounds to ensure product for future trials!

Marijuana and Brain Abnormalities?

Medical Marijuana: Harvard Study Claims Recreational Legal Weed Causes ‘Significant Brain Abnormalities’

Scientist Blasts Report Linking Casual Pot Smoking With Brain Abnormalities

Posted: 04/22/2014 2:58 pm EDT  |  Updated: 04/22/2014 3:59 pm EDT
Marijuana and Brain Abnormalities?

40 people aged 18-25 years. Half used marijuana at least once weekly (starting 14-18 years old), other half did not use. For marijuana users, found greater density values in the nucleus accumbens and amygdala.

Gilman JM, et al. Cannabis Use Is Quantitatively Associated with Nucleus Accumbens and Amygdala Abnormalities in Young Adult Recreational Users. The Journal of Neuroscience April 16th 2014
Marijuana and Brain Abnormalities?

Limitations

- No measures of cognitive performance or any other behaviors. Impossible to interpret meaning of any brain measure differences.

- Marijuana group used multiple other substances; impossible to disentangle the effects of marijuana from those of other drugs.

- Association is not causation! Authors repeatedly and explicitly state a causative relationship between marijuana use and anatomic changes, only to state 2nd last paragraph no causative relationship can be concluded due to the cross-sectional design!
FDA Approved Cannabinoids

Dronabinol
- Schedule 3
- Trans isomer of synthetic THC
- FDA indications:
  - Chemo induced n/vomiting
  - Anorexia associated weight loss with AIDS

Nabilone
- Schedule 2
- Synthetic THC mimic
- FDA indication:
  - Chemotherapy induced n/vomiting
Sativex (Nabiximols)

Features in American Academy of Neurology Guideline On Cannabis in MS

- Each spray—fixed dose of THC 2.7mg and CBD 2.5mg, derived from plants (not synthetic)—a tincture
- Launched in 27 countries (incl. UK and Canada) for MS spasticity
- In development for cancer pain and neuropathic pain
- Side effects—dizziness (25%), drowsiness (8.2%) and disorientation (4%)
- Otsuka Pharmaceuticals has exclusive license to develop and market Sativex in the US
- Oral CBD only product in trials

www.gwpharm.com
Marijuana in Clinical Trials

Nearly all oral administration

- Nabiximols: Oromucosal spray
- Dronabinol: Capsule
- Nabilone: Capsule
- THC: Capsule, smoked
- Cannabidiol: Capsule
- Cannabis: Vaporized, smoked
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 Schmidtkofer, MSc; Marie Westwood, PhD; Jos Kleijn, MD, PhD

79 RCTs were included (No. or reports [No. of patients])

28 Nausea and vomiting due to chemotherapy (37 [1772])
28 Chronic pain (63 [2454])
14 Spasticity due to multiple sclerosis or paraplegia (33 [2280])
  4 HIV/AIDS (4 [255])
  2 Sleep disorder (5 [54])
  2 Psychosis (9 [71])
  2 Tourette syndrome (7 [36])
  1 Anxiety disorder (1 [24])
  1 Glaucoma (1 [6])
  0 Depression
## Cannabinoids for Medical Use
### A Systematic Review and Meta-analysis

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

### RCTs were included (No. or reports [No. of patients])

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of RCTs</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting due to chemotherapy</td>
<td>28</td>
<td>1772</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>28</td>
<td>2454</td>
</tr>
<tr>
<td>Spasticity due to multiple sclerosis or paraplegia</td>
<td>14</td>
<td>2280</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>4</td>
<td>255</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>2</td>
<td>54</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2</td>
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</tr>
<tr>
<td>Tourette syndrome</td>
<td>2</td>
<td>36</td>
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<tr>
<td>Anxiety disorder</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### Treatment Regimens
- 13 Nabiximols
- 5 Nabilone
- 4 smoked THC
- 3 THC oromuosal spray
- 2 dronabinol
- 1 Cannabis vaporized
- 1 active comparator - nabilone + amitriptyline

Cannabinoids and Chronic Pain
Outcome: 30% or more reduction in pain

8 Trials, 6 neuropathic pain, 2 cancer pain
Chronic Pain and Marijuana

- High quality 2011 systematic review- 7/9 trials of chronic neuropathic pain (not MS)- significantly greater analgesic effects for cannabinoids V placebo. Effect sizes modest and trials short duration

- Earlier (2009) systematic review- chronic cancer and non cancer pain (pooled analysis) positive for cannabis- although concern for bias in included trials

- 2013 study- low dose vaporized cannabis significantly improves neuropathic pain (mix of peripheral and central pain, 39 subjects)

Farrell M et al. Should doctors prescribe cannabinoids? BMJ 2014;348:g2737
Chronic Pain and Marijuana

- HIV related painful peripheral neuropathy—Two randomized trials—evidence for efficacy with smoked cannabis; small groups of participants smoked cannabis for a total of 5 days and reported improvement in pain scores that were significantly better than those with placebo.


Cannabinoids and Chronic Pain

New Setback for Medical Marijuana Spray

October 28, 2015

By Pat Anson, Editor

A British drug maker has announced more disappointing results from clinical studies on the use of a medical marijuana spray to treat cancer pain.

GW Pharmaceuticals (NASDAQ: GWPH) said results from two new Phase III studies showed that its Sativex oral spray worked no better than a placebo in treating cancer pain. That was the same finding the company reported in January from an earlier study involving nearly 400 patients in the United States, Mexico and Europe.

However, patients in the U.S. did show “statistically significant improvement” in their pain levels when Sativex was taken along with an opioid pain medication. GW and its partner, Otuska Pharmaceutical, have requested a meeting with the U.S. Food and Drug Administration to explain that finding. Sativex is getting a “fast track” review from the agency as a treatment for cancer pain.

“In light of the missed primary endpoint in the first trial earlier this year, these additional results are not a surprise. Nevertheless, we are encouraged by data across the trials which consistently show positive outcomes for U.S. patients when analysed as a separate cohort,” said Justin Gover, GW’s Chief Executive Officer.
Cannabidiol significantly improved anxiety compared to placebo.

Moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity.

There was low-quality evidence associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome.
## AAN Guideline On Cannabis in Multiple Sclerosis

<table>
<thead>
<tr>
<th>CAM intervention</th>
<th>Number and class of studies</th>
<th>MS types studied</th>
<th>Outcome</th>
<th>Recommendation level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cannabinoids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OCE</strong></td>
<td>2 Class I,(^{13,14}) 1 Class II,(^{17}) 1 Class III(^{18})</td>
<td>RRMS, SPMS, PPMS, MSU</td>
<td>Symptoms of spasticity, pain</td>
<td>A Effective</td>
</tr>
<tr>
<td></td>
<td>1 Class I(^{13})</td>
<td>RRMS, SPMS, PPMS</td>
<td>Signs of spasticity (short-term), tremor (short-term)</td>
<td>B Ineffective</td>
</tr>
<tr>
<td></td>
<td>1 Class II(^{17})</td>
<td>MSU</td>
<td>Signs and symptoms of spasticity (long-term)</td>
<td>C Effective</td>
</tr>
<tr>
<td></td>
<td>2 Class I,(^{13}) 1 Class II(^{16})</td>
<td>RRMS, SPMS, PPMS, MSU</td>
<td>Bladder symptoms, urge incontinence</td>
<td>U</td>
</tr>
<tr>
<td><strong>Synthetic THC</strong></td>
<td>1 Class I,(^{13}) 1 Class II(^{17})</td>
<td>RRMS, SPMS, PPMS</td>
<td>Symptoms of spasticity, pain</td>
<td>B Effective</td>
</tr>
<tr>
<td></td>
<td>1 Class I(^{13})</td>
<td>RRMS, SPMS, PPMS</td>
<td>Signs of spasticity (short-term), tremor (short-term)</td>
<td>B Ineffective</td>
</tr>
<tr>
<td></td>
<td>1 Class II(^{17})</td>
<td>MSU</td>
<td>Signs and symptoms of spasticity (long-term)</td>
<td>C Effective</td>
</tr>
<tr>
<td></td>
<td>1 Class I,(^{13}) 1 Class II,(^{16}) 1 Class III(^{19})</td>
<td>RRMS, SPMS, PPMS, MSU</td>
<td>Bladder symptoms, urge incontinence, central neuropathic pain</td>
<td>U</td>
</tr>
<tr>
<td><strong>Sativex oromucosal spray</strong></td>
<td>3 Class I,(^{23-25}) 2 Class II,(^{26,27}) 3 Class III(^{28,30})</td>
<td>MSU</td>
<td>Symptoms of spasticity, pain, urinary frequency</td>
<td>B Effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Signs of spasticity, incontinence episodes</td>
<td>B Ineffective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tremor</td>
<td>C Ineffective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anxiety/sleep, cognition, QOL, fatigue</td>
<td>U</td>
</tr>
<tr>
<td><strong>Smoked cannabis</strong></td>
<td>2 Class III(^{31,32})</td>
<td>RRMS, SPMS, MSU</td>
<td>Spasticity, pain, balance and posture, cognition</td>
<td>U</td>
</tr>
</tbody>
</table>

AAN Guideline On Cannabis in Multiple Sclerosis

- May offer oral cannabis extract (OCE) for MS related symptoms of spasticity and pain (excluding central neuropathic pain) Level A and THC (Level B)
- OCE probably ineffective for improving objective spasticity measured (short term) or tremor (Level B)
- Might offer Sativex oromucosal cannabinoid spray to reduce symptoms of spasticity, pain and urinary frequency (Level B)

Efficacy, tolerability and safety of Cannabinoid Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials

Mary-Ann Fitzcharles¹,², Peter A. Ste-Marie², Winfried Häuser³,⁴, Daniel J. Clauw⁵, Shahin Jamal⁶, Jacob Karsh⁷, Tara Landry⁸, Sharon LeClercq⁹, Jason J. McDougall¹⁰, Yoram Shir², Kam Shojaian⁶,¹¹, Zach Walsh¹²

Cannabis in Rheumatology

- 4 Short term studies, total of 201 patients (58 Rheumatoid arthritis, 71 Fibromyalgia, 74 Osteoarthritis)
- Nabiximols- RA positive study
- Nabilone 2 trials in FM
  One study-improved pain at 4weeks
  Second non-inferiority with amitriptyline same outcome
- Fatty acid amide hydrolase (FAAH) inhibitor V Naproxen V placebo- 74 pts OA stopped for futility
- Cannabinoids- statistically significant effect on pain in 2 studies, sleep in 2 and improved quality of life in 1 study
- Dizziness, cognitive problems and drowsiness common
- Review suggests evidence insufficient to recommend at this time

Cannabinoids in Epilepsy

- Despite >20 anti-seizure meds, 30% of people with epilepsy still have seizures
- Preliminary studies identified defects in endocannabinoid system in those with epilepsy (lower levels of CSF anandamide)
- Historically only 4 placebo-controlled studies using cannabinoids and epilepsy problems with methodology, poor power and lack of blinding

- Cannabidiol (CBD) - anti-seizure - independent of endocannabinoid system
- THC and synthetic THCs can provoke seizures

Cannabinoids in Epilepsy

Editorial

Medical marijuana for epilepsy: Winds of change

Nearly 3 million people in the United States live with epilepsy, and over one million people live with uncontrolled seizures of some type [1]. As a result, those one million people with uncontrolled epilepsy will try almost anything to get these seizures to stop from numerous medications with side effects, difficult diets, surgical intervention, and implantable devices. Given the situation, it follows that one is often left to deal with one’s own wits and creativity in figuring out how to best to help themselves or a loved one with a complex medical condition like epilepsy in an increasingly complicated health-care system in order to attain a good quality of life. As such, this opens a doorway for untested, uncertain therapies and for misinformation and misunderstanding to occur which, in turn, leads to experimenting with unproven treatments conducted by patients themselves in order to help themselves and their loved ones. This is the current story of cannabis for epilepsy.

This issue places the epilepsy community at a medical legal ground zero in resolving this situation, and this study, if anything, highlights the failure of the health-care system as a whole to grapple with better management of epilepsy as it deals with our most vulnerable citizens — our children. Amazingly, like any good parents who want to ameliorate suffering in their kids, they have taken matters into their own hands delivering an unproven treatment without solid information on the safety and viability of medical cannabis for epilepsy. It is providential and positive that they have been able to receive benefit but tragic that they had to conduct their own trial without help in order to accomplish this.

This survey illuminates the nuanced science of cannabis. When cannabis is ingested or smoked, it two potential important compounds with opposite enter the CNS; delta-9-tetrahydrocannabinol, the psycho-
Open label study—‘compassionate access’ by investigators independent from GW Pharma

Severe treatment resistant childhood onset epilepsy

N=137 in efficacy analysis

First prospectively collected data on CBD and epilepsy

Results

Dravet syndrome
Median reduction in motor seizures 49.8%
50% had a 50% or more reduction
13% (n=4) seizure free

Lennox-Gastaut Syndrome
68.8% reduction in monthly atonic seizures
Last 4 weeks 21% (n=3) seizure free
In those with motor and atonic seizures 36.8% and 44% (n=21) reductions.
Clinical evidence with Cannabinoids & Pain

- Studies on the use of cannabinoids for pain started in the 1970’s
- There are no blinded studies on the use of cannabinoids for headache

Experimental evidence with Cannabinoids & Headache

Goadsby et al demonstrated that an endogenous cannabinoid receptor ligand—anandamide was able to inhibit dural blood vessel dilation from electrical stim, CGRP, nitrous oxide and capsaicin and this was reversed by a cannabinoid antagonist.

Conclusions

Moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity.

There was low-quality evidence associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome.
Retrospective observational study - Medical Marijuana clinic
Identified 262 pts between 1/2010-9/2014 with migraine
121 had a follow up visit - included 68% previous or current marijuana use on first visit
Primary outcome: number of migraines/month

- Headaches/month reduced 10.4–4.6 (p<0.01)
- 85% pts decrease in frequency, 15% same and 3% increase in freq.

Forms - Vaporized 42pts, edible 66 pts, smoked 65 pts, topical 15 pts

Cannabis for Glaucoma?

- All glaucoma therapies target IOP
- Systemic and topical THC reduce IOP, CB1 effect experimentally
- Likely by reducing secretion
- Most studies – IOP lowering properties resolve within hours

- One trial – 6 subject crossover trial single dose THC 5mg V cannabidiol 20mg V cannabidiol 40mg V placebo all sublingual - only THC reduced IOP
- No good trial evidence
- Treatment is long term, may not be suited to cannabis

Cannabinoid receptors occur throughout the vertebrates—hence are evolutionarily ancient.

Genes for such a receptor were found in the deuterostomian invertebrate Ciona intestinalis, but not in protostomian invertebrates (e.g., Drosophila).

Likely that cannabinoid receptors developed first in deuterostomian invertebrates.
THE END!