Medical Marijuana: Getting In the Weeds

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AGENDA

What is MEDICAL Marijuana (MMJ)?
Is Marijuana Medicine?
Marijuana vs Industrial Hemp
Why Marijuana, Why Now?
Effects and Side Effects of Marijuana
Diseases and Medical Marijuana: What the Studies Show
Smoking and Misuse of Marijuana
Conclusion
What is MMJ?

Dried flowers and leaves of the Cannabis (marijuana) plant taken for a desired medical purpose.

SYNTHETIC "MARIJUANA" FLOODS TAMPA BAY AREA

"...What makes spice dangerous is how easy it is to get, its inexpensive price and the difficulty of following through with prosecution. While it is called synthetic marijuana, officials say it has nothing to do with the leafy drug that is being legalized for medical use and decriminalized in some U.S. states and cities.

Synthetic marijuana is made by taking dried plant material and soaking it in ever-changing chemical combinations. Packets of the drug used to be available in convenience stores alongside packs of chewing gum and candy bars, and sometimes still are, O’Connor said.

Those packets often are rolled into individual spice cigarettes, which sell on the street for $1 or $2 each.

They don’t know what they’re taking ..."

Associated Press March 28, 2016

SYNTHETIC "MARIJUANA" IS NOT MEDICAL MARIJUANA

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PHARMACEUTICAL CANNABINOIDS ARE NOT MEDICAL MARIJUANA

Synthetic Cannabinoids
Made in laboratories; examples include FDA approved Marinol® (dronabinol) and Cesamet (nabilone)

Marinol®: Synthetic Oral THC
Cesamet®: Synthetic Oral THC Analogue

Phytocannabinoids
Found in the plants, contains hundreds of cannabinoids, most notably THC and CBD

Marinol® (dronabinol)
Sativa® (Canada/UK): Herbal Cannabis Extract

MARIJUANA REFERS TO DRIED FLOWERS AND LEAVES OF CANNABIS PLANT

- Various species but C. sativa and indica most common for medical marijuana
  - 1973 HY: Marijuana legalized medically
  - 1981 AD: Codeine derived-medicinal compound in US Pharmacopoeia
  - 1997 AD: Cannabis in the United States

- Approximately 100M adult Americans have used marijuana and current use rate is reported 17.4M

- 1.1+M legal medical marijuana patients registered in the United States (as of Oct 2014, procon.org)

- Schedule I Federal Controlled Substance
  - Similar to marijuana, heroin, cocaine, LSD
  - No legitimate medical use, lack of accepted safety under medical supervision, and a high potential for abuse

- Dried flowers, leaves and stems are usually smoked, but can be vaporized or cooked for ingestion of the extracts

- Alternative methods of administration avoid combustion and are considered less harmful to the lungs than smoking

MEDICAL MARIJUANA PRODUCTS

The New Smoking

- Smoking is a natural irritant to the lungs
- Alternative methods avoid combustion and maybe considered less harmful to the lungs
- Diluted tetrahydrocannabinol vapor poses high potential for addiction, cancer, seizures, and other dangerous toxins

EDIBLES

- Edibles take longer to start. Do not ingest more than needed. Edibles deaths in Colorado
- Effects last longer: edible 6-8 hours, smoking 1-2 hours
- Dosage not accurate; analysis only 17% accurate THC levels, 60% lower, 23% higher

CREAMS/OILS

- Creams, CBD, coconut oil, hemp oil, lanolin, butter
- Effects less detectable urine drug test
- May not be detectable on urine drug test

Topical Creams

- Contain: THC, CBD, coconut oil, hemp oil, lanolin, butter
- Problems compounding exist for these products

Oral Oils

- CBD Oil, MCT Oil

PHARMACEUTICAL CANNABINOIDS ARE NOT MEDICAL MARIJUANA
Main Cannabinoid Chemicals

Anandamide
- A natural messenger chemical present in the brain at low levels
- Endocannabinoid role in pain, depression, appetite, memory and fertility

Delta-9-tetrahydrocannabinol (THC)
- Most psychoactive cannabinoid of >200 identified
- Interacts with cannabinoid receptors in the body giving the effects of feeling high
- High concentrations in sativa species, moderate in indica species

Cannabidiol (CBD)
- Nonpsychoactive; interacts differently with receptors along with a serotonin receptor giving the effects of feeling relaxed and heavy aka stoned
- Higher concentrations in indica species vs sativa species

INDUSTRIAL HEMP VS MEDICAL MARIJUANA

INDUSTRIAL HEMP
- Low THC <0.3% C sativa plant bred for fiber for clothing, construction, oils and topical ointments (not psychoactive)
- 2014 Fed Farm Bill allows university and state departments to grow industrial hemp
- Sale, production and distribution of CBD products from imported raw material industrial hemp is legal
- Cannabinoids in industrial hemp, including oil, were never scheduled under the Controlled Substances Act
- Raw materials shipped to the US obtained from Europe
- Several CBD products used for medical conditions (no medical claims allowed FDA)

MEDICAL MARIJUANA
- CBD/THC (THC higher than 0.3%)
- Current THC is 18% to 30%
- Reports of pesticides greater (6X) than that seen in food
- House members restrict DEA from using funds to go after medical marijuana operations legal under state laws
- Almost half of states legalized medical use; more expected to legalize recreational use
- Unclear if any federal bills will follow suit

Why the Interest?
23 STATES & DC LEGALIZED MEDICAL MARIJUANA (YEAR PASSED)

Alaska 1998
Arizona 2010
California 1996
Colorado 2000
Connecticut 2012
D.C. 2010
Delaware 2011
Hawaii 2000
Illinois 2013
Maine 1999
Maryland 2014
Massachusetts 2012
Michigan 2008
Minnesota 2014
Montana 2004
Nevada 2000
New Hampshire 2013
New Jersey 2010
New Mexico 2007
New York 2014
Oregon 1998
Rhode Island 2006
Washington 2004
Vermont 2004
Wisconsin 2009

CBD Legislation: AL, DE, FL, GA, IA, KY, MS, MO, NJ, OK, SC, TN, TX, UT, VA, WI

Despite legislation by almost half of the United States, marijuana use is still illegal at the federal level, which considers marijuana a schedule I controlled substance.

CONSUMER SITES ADVOCATE FOR MMJ

Why Medical Marijuana?

- Opioids in disfavor and under scrutiny
  - CDC: 44-78 people die every day in the United States from overdose of prescription painkillers; many more become addicted
  - Amount of Rx opioids dispensed nearly quadrupled (1999-2013), yet no change in amount of pain Americans report
  - Rx painkillers have killed more than 16,000 people in the US in 2013

- Lack of alternative analgesics

Recreational use of marijuana study reports:

- No respiratory depression (person stops breathing) with marijuana when used alone* vs opioids which can cause respiratory depression when used alone

* There are no reports of fatal overdoses in the epidemiological literature

BUT

- Doubling the chance of a driving accident
- Dependence can develop in 1 in 6 adolescents and half of daily cannabis users
- Increases in adverse effects in THC and withdrawal symptoms can occur if suddenly stopped
- Strongly associated with use of other illicit drugs

- Negatively impacts IQ
- When related to adolescence and continued into adulthood
- Effect on cognitive function and academic performance

- Smoking marijuana has been associated with an increased risk of cardiovascular side effects and stroke, cardiac in middle age and older

* 279 deaths where marijuana was involved

**Effects and Side Effects**

**EFFECTS OF MARIJUANA**

**THC**
- Mood changes such as anxiety or depression
- Cognition effects
  - Decreased concentration
  - Short-term memory loss
  - Decreased attention span
  - Paranoia
  - Time distortion
- Decreased spasticity
- Increased appetite
- Analgesia
- Abuse and dependence potential
  - Psychological and physical

**CBD**
- Synergistic effect with THC reducing THC-associated anxiety and paranoia
- Anxiolytic
- Antipsychotic
- Anticonvulsant
- Neuroprotective properties

1960s THC concentration was only 1% to 1.5%, now, THC is 16% to 33%


PERCEIVED SAFETY OF MARIJUANA VS OPIOIDS

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**SIDE EFFECTS OF SMOKING MARIJUANA**

- Wadsworth et al, 2006
  - Short-term memory problems
  - Impaired thinking and ability to perform tasks requiring mental alertness
  - Loss of balance and motor function (e.g., coordination)
  - Decreased ability to concentrate
  - Changes in sensory perception
  - Decreased reaction time

- Ammerman et al, 2015
  - Increased heart rate
  - Increased blood pressure
  - Dry mouth
  - Increased appetite, thirst
  - Drowsiness
  - Anxiety, insomnia, panic attacks
  - Hallucinations
  - Conjunctival injection

**LONG-TERM EFFECTS OF SMOKING MARIJUANA**

- Increased risk of lung cancer
  - 3 to 4 joints = 20 tobacco cigarettes
- Increased risk of psychosis
  - 3 year study (535 patients)
  - 54% schizophrenia-spectrum disorder
- Increased risk of periodontal disease
- Younger users: decline in IQ (permanent cognitive impairment)
- Males
  - Suppression of testosterone secretion decreasing libido and/or gynecomastia
  - Decreased sperm count and motility leading to an increased chance of infertility
- Withdrawal syndrome
  - Restlessness, insomnia, anxiety, aggression, tremors
  - Daily dose of 180 mg THC (1-2 joints) for 11-21 days

**EFFECTS OF SYSTEMIC CBD: NOT ALL IS GOOD**

- Side Effects of CBD
  - Effects on the immune system may be possible, worsening of disease progression – HIV infection, tumor genesis, and metastases
  - Sedation
  - Question effects on blood sugar
  - Feeling heavy
  - Overdoses in monkeys: tremors, convulsions, vomiting, sedation to prostration in 30 minutes, cardiac failure

- Drug Interactions - CBD
  - May cause drug interactions and increase or decrease their effects or make them toxic
  - Significant number of drug interactions to make it a concern
  - CBD could interact with anticancer drugs
  - CBD possible interaction with other pain meds like NSAIDs (e.g., Motrin, Aleve)
ADVERSE EFFECTS OF MARIJUANA ON HEALTH AND WELL-BEING

<table>
<thead>
<tr>
<th>ADVERSE EFFECT</th>
<th>LEVEL OF EVIDENCE</th>
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<tbody>
<tr>
<td>Addiction to drugs</td>
<td>HIGH</td>
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<tr>
<td>Low lifetime achievement</td>
<td>HIGH</td>
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<tr>
<td>Increased motor vehicle accidents</td>
<td>HIGH</td>
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<tr>
<td>Chronic bronchitis</td>
<td>HIGH</td>
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<tr>
<td>Abnormal development of brain</td>
<td>MEDIUM</td>
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<tr>
<td>Progression to other drug use</td>
<td>MEDIUM</td>
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<tr>
<td>Comorbid anxiety or depression</td>
<td>MEDIUM</td>
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<tr>
<td>Schizophrenia</td>
<td>MEDIUM</td>
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<tr>
<td>Lung cancer</td>
<td>LOW</td>
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NON-MEDICAL MARIJUANA AND PRESCRIPTION DRUG MISUSE CONTINUES IN THE UNITED STATES

- Lab data (22,000+ UDTs) correlation between marijuana and prescription drug use in national population
- Marijuana most frequently detected non-prescribed drug in >26% of patients who do not use medications as prescribed
- Marijuana most frequently detected drug in the nation’s workforce. Quest March 2013 drug test index report
- Approximately 45% of patients who use recreational marijuana also used other non-prescribed drugs (i.e., sedatives and narcotics)
- 37% of medical marijuana users misused other drugs
The laws in many states define the medical conditions, circumstances and methods of consumption in which an individual can secure and use medical marijuana. Pennsylvania allows the following "qualified medical conditions":

- Cancer
- HIV or AIDS
- Amyotrophic lateral sclerosis (ALS, Lou Gehrig’s Disease; paralysis)
- Parkinson’s Disease
- Multiple sclerosis (MS)
- Spinal cord damage spasticity
- Epilepsy and intractable seizures
- Inflammatory Bowel Disease and Crohn’s Disease
- Neuropathic Pain
- Huntington’s Disease
- Posttraumatic stress disorder (PTSD)
- Glaucoma
- Sickle Cell Anemia
- Severe-chronic or intractable pain (neuropathic OR traditional therapy ineffective …)
- Autism

The above list of medical conditions is broad, and in most cases not supported by solid clinical research. Any research that has been done used smoked marijuana; studies are needed with use of edible products, extracted oils, tinctures and topical ointments.


Studies

- Short-Term Effects of Cannabis Therapy on Spasticity in MS
- Use and Misuse of Cannabis
- Treatment of Spasticity of Multiple Sclerosis in Pooled HIV Neurology
- Impact of Repeat-Filled Canabis, Treatments on Driving Abilities
- Mechanism of Cannabidiol: A Non-Cannabinoid Effect of Cannabinoids
- Effects of Medical Cannabinoids on Cognitive Function in AIDS
- Analgesic Efficacy of Dronabinol
- Efficacy of Intravenous Cannabinoids in Dementia, Parkinson’s Neurology
- A Double-Blind, Active Placebo-Controlled, Crossover Trial of the Antinociceptive Effects of Intravenous Marijuana on Neuropathic Pain: Comparison with Opiates in Opiates, Cognition, and Psychomotor Performance
- The Analgesic Effect of Intraperitoneal Cannabinoids on Neuropathic Pain
- Spinal Cord Injury
- Depression in HIV-Infected Comorbidities Delays Systemic
- Cannabis for Treatment of HIV-Related Peripheral Neuropathy

LOOKS GOOD BUT ...

1. 30 pts, many drop outs, side effects
2. 10 HIV pts, 2 day pilot study, 2006 not published
3. 28 pts, with opioids, 2 wks, 2 dropouts, measure limited by confusion and sedation
4. ACS complete but no results
5. Rat headaches
6. Preclinical evidence, endocannabinoid responses to anandamide indicate no change
7. AIDS preclinical cell immunity study 2004
8. 15 healthy volunteers “suggests window of modest analgesia for smoked cannabis. … lower dose decrease pain”
9. 10 patients … preliminary evidence to support further research …”
10. 36 patients … use of MJ as effective in both method smoking and acute cognitive effects
11. 52 for pain relief. Don’t jump to conclusions …
12. 14/18 subjects preferred vaporizing to smoke
13. 52% smoked MJ had >30% reduction in NP vs. 24% with placebo.
Use in Epilepsy

- Interest in use for resistant epilepsy the result of a mix of science, politics, and social phenomena
- Anecdotal evidence (no controlled trials) of seizure control, but results with CBD encouraging; might be considered under close physician supervision after failure of all conventional therapies
- Evidence for medical marijuana being harmful to developing brain (e.g., schizophrenia)

Future Research Funded

- Colorado Board of Health awards $8 M to study medical marijuana’s therapy potential
- First government money for efficacy research rather than just looking for negative effects
- Funded by state medical marijuana patient user fees—medical use legalized in 2000, recreational use in 2012
- Other studies: anxiety, ADHD, substance abuse, epilepsy, pain, nausea, arthritis, PTSD, schizophrenia, sickle cell disease, sleep apnea, spasticity/MS (https://ClinicalTrials.gov)

LACK OF EVIDENCE FOR SMOKED MEDICAL MARIJUANA

Much of the evidence is anecdotal; few double-blind, randomized, controlled trials; most of poor quality as a result of Federal Class I designation

American Medical Association (AMA)
- Despite the public controversy, less than 20 small randomized controlled trials of short duration involving ~300 patients have been conducted over the last 35 years on smoked cannabis.
- Large variability in specific cannabinoids in various medical marijuana products
- Reduce the schedule and conduct more research

Institute of Medicine (IOM)
- Smoking marijuana is not recommended. The long-term harm caused by smoking marijuana makes it a poor drug delivery system, particularly for patients with chronic illnesses.
- Development of non-smoked, reliable delivery systems and testing needed

1. Preclinical (animal) testing
2. An investigational new drug application (IND) outlines what the sponsor of a new drug proposes for human testing in clinical trials
3. Phase 1 studies typically involve 20 to 80 people
4. Phase 2 studies typically involve a few dozen to about 300 people
5. Phase 3 studies typically involve several hundred to about 3,000 people
6. The pre-NDA period, just before a new drug application (NDA) is submitted. A common time for the FDA and drug sponsors to meet
7. Submission of an NDA is the formal step asking the FDA to consider a drug for marketing approval
8. After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed
9. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor’s research on the drug’s safety and effectiveness
10. The FDA reviews information that goes on a drug’s professional labeling (information on how to use the drug)
11. The FDA inspects the facilities where the drug will be manufactured as part of the approval process
12. FDA reviewers will approve the application or issue a complete response letter
13. Post-marketing surveillance

PHARMACEUTICAL CANNABINOIDS

Synthetic Cannabinoids
Made in laboratories; examples include FDA approved Marinol® (dronabinol) and Cesamet® (nabilone)

Marinol®: synthetic oral THC
- Schedule III
- Relieve nausea/vomiting from chemotherapy and loss of appetite in patients with HIV

Cesamet®: synthetic oral THC analogue
- Schedule II
- Believed to be more potent than THC
- Nausea/vomiting associated with chemotherapy

Phytocannabinoids – Cannabis
Found in the plants; contains hundreds of cannabinoids, most notably THC and CBD

Sativex® (Canada/UK): herbal Cannabis extract (THC/CBD, 1:1)
- Sublingual spray adjunct treatment central neuropathic pain in MS and cancer pain
- Rapid acting, easy to use
- Study in the US showed not better than placebo for pain


Summary
- In an environment of opioid scrutiny and critical use, states are moving to approve medical marijuana for pain and certain critical conditions
- THC can decrease pain in mid-range (but not high) doses, and also leads to serious risks of dependence, and excessive CNS side effects with cognitive decline
- There are no quality clinical studies demonstrating the medical benefits of smoked marijuana, edibles or other oral forms and cannabinoid use
- Despite medical marijuana legalization in 23 states and DC and recreational use in 4 states, marijuana remains a Federal Schedule I controlled substance—still illegal to manufacture, possess and use under federal law
- Conflict between state and federal law creates confusion
- Physicians are mandated to adequately treat pain, yet may be sanctioned by their licensing medical boards
- Adverse effects and legal implications may outweigh the benefits of medical marijuana in some cases
Physicians should not recommend that patients use marijuana for medical purposes because it is a dangerous, addictive drug and is not approved by the FDA. —American Society Addiction Medicine

Despite legalization by several states, marijuana use is still illegal in the United States at the federal level (which considers marijuana a schedule I controlled substance), and individuals prescribing or using marijuana for medical use are at risk for prosecution. —UpToDate. Online database. April 2016

“Cannabinoids—Not recommended for pain … there are no quality studies supporting cannabinoid use, and there are serious risks … It is very difficult to do controlled studies with a drug that is psychoactive because it is hard to blind to these effects … high doses increase pain … [and] declines in cognitive performance … integral to a patient’s work and lifestyle … adding a cannabinoid to opioid therapy … more study needed.

Smoking anything is unacceptable … Cannabis is unstable and unpredictable and the drug should be subject to the same standards that apply to other medications. For every disease and disorder for which marijuana has been recommended, there is a better, FDA-approved medication.” —Work loss Data Institute Apr 2016

Questions

Bibliography


BIBLIOGRAPHY